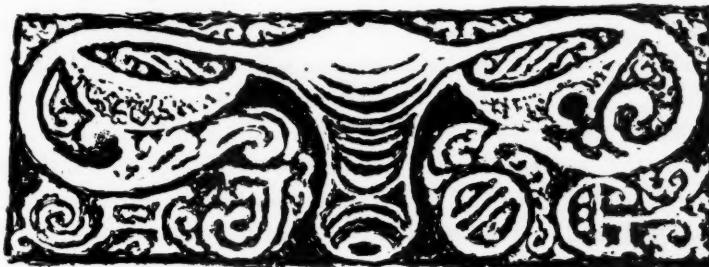


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ANOTHER five years have elapsed in the continued progress of this publication as a representative organ in the special field to which it is devoted. During these thirty years since its founding, the JOURNAL has been increased in size several times to accommodate the larger number of contributions submitted for inclusion in its pages. These necessarily are limited to those emanating from the United States and Canada and those from foreign sources have been declined in maintaining the policy that this is an American and not an international journal.

Several members of the Advisory Editorial Board and the Publication Committee have passed away since the last Anniversary Issue in 1945, including Dr. Robert T. Frank, the Editor of the Book Review Department, whose duties have devolved upon Dr. Philip F. Williams. To the latter, as well as the members of the abstracting staff, and to my associate editors, Drs. Howard C. Taylor and William J. Dieckmann, an expression of appreciation is due for their devoted labors. The C. V. Mosby Company has continued to give

efficient and liberal attention to the difficult situation in the mechanical and business management for which it is to be highly commended. We also owe a word of thanks to Dr. Robert L. Dickinson for the specially designed title page. And, last, to the many physicians who have contributed their articles to its pages, we owe this acknowledgment of their support.

George W. Kosmak, M.D.

American Gynecological Society

Transactions of the Seventy-Third Annual Meeting
May 11 to 13, 1950, at White Sulphur Springs, West Virginia

THE LIFE OF JAMES MARION SIMS*

Presidential Address

JOSEPH L. BAER, M.D., CHICAGO, ILL.

AT OUR meeting last year, while I was still overwhelmed by the honor of becoming the custodian of the "gavel," the doorknob from the office of Ephraim McDowell, my dear friends and predecessors took pains to weigh me down still further. Like ghouls they harassed me with the necessity of selecting and delivering a Presidential Address.

The selection of the subject matter was easier than I had anticipated. Nineteen forty-nine was the centennial of Sims' cure of vesicovaginal fistula. Today the man's name and fame survive, but his life story is almost forgotten.

The ability to breathe life into a personage long since dead is rare indeed. Through the ages the stage has provided the ideal setting for such an achievement. Today I propose merely to depict the life story of the Father of Gynecology, James Marion Sims, dwelling upon his personal attributes, without benefit of scenery or reenactment of the incidents and events which set this man apart then and now.

Sims' life and career are so replete with sunshine and storms, with contentment and restless urge, with love and frustration, with religious fervor and bitter disillusionment, with grave illnesses and stupendous achievement, with dogged determination and semiexpatriation, that they could be the theme for a great drama in the style of a Greek tragedy.

James Marion Sims was born in Lancaster County, South Carolina, January 25, 1813, and died in New York City, November 13, 1883. His paternal ancestors were English colonists in Virginia. His mother, Mahala Mackey, was Scotch-Irish. Her people also were early colonists. All Sim's forebears were farmers. John Sims, the father, lived to be seventy-eight. The mother was one and one-half years younger, black eyed, and with red hair. Marion, the third child, was the first boy in a family of nine. His mother was skilled in all the household activities and well educated. His father had no education but finally went to school for a few months after Marion was six months old. Indeed, thereafter

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

he became an accountant and bookkeeper, a hotel keeper, a surveyor, a colonel of Militia and served in the War of 1812 and in the Confederate Army when he was seventy-three.

Too poor to educate all their children, they concentrated on Marion, the oldest son. It is difficult to evaluate the effect this singling out may have had on the character of this sensitive lad. He did develop a strong sense of family unity and devotion as is shown when he in turn became the head of a large family.

Marion's stories of his succession of private teachers with whom he boarded emphasize that flogging was the basic approach to teaching—Marion writes of himself as one of the good boys but he was whipped just the same. His autobiography is fascinating. It is filled with anecdotes of his childhood and youth. It covers his entire life up to 1863, twenty years before he died.

His remarkable memory is evidenced by the fact that this autobiography was not written until the year of his death. It reveals much of the background and the incidents which shaped his character. Sims was a little fellow. At eighteen he weighed only 108 pounds and stood five feet, eight and one-half inches. In childhood he was timid though not cowardly. He never learned to swim but became an excellent rider and hunter. His giant father excelled in these accomplishments. He rode to hounds, attended cock fights, and played billiards very well. His religious mother abhorred these activities and because of this influence Sims never took up any of these diversions. Neither father nor son drank or used tobacco.

Sims tells one anecdote which indicates how receptive he was to pointed object lessons. It occurred when Sims was eight years old. His father's partner, speaking of an ill-smelling weed, asked Marion whether its name was Jimson weed or Jamestown weed. Marion said "Jimson," which was wrong, and got a lecture on being sure before making a positive statement. This lesson he never forgot.

Marion's formal schooling began at Columbia College, Columbia, South Carolina, where he studied from October, 1830, to December, 1832. He was now nineteen years old, deeply in love with his childhood sweetheart, Eliza Theresa Jones, aged seventeen, and hopelessly poor. It was just at this critical time in Sims' formative years that his strong-minded and understanding mother died at the age of forty. The mutual love of the two young people, the tragedy of their enforced separation for three years, Mrs. Jones' grudging acceptance of Marion as a suitor, his struggles to attain a livelihood, and their ultimate marriage and lasting happiness offer another facet of Sims' steadfastness of purpose.

Educated young men had to select the law, the ministry, or medicine. Marion's mother, a staunch Presbyterian, wanted him to go into the ministry. His father, by now a respected and self-educated citizen who owned a store and a tavern, wanted his son to take up law. Marion had no urge for either profession and so perforce had to study medicine, much to his father's disappointment and disgust, expressed in these words:

"It is a profession for which I have the utmost contempt. There is no science in it. There is no honor to be achieved in it; no reputation to be made,

and to think that *my son* should be going around from house to house through this country, with a box of pills in one hand and a squirt in the other, to ameliorate human suffering, is a thought I never supposed I should have to contemplate."

Happily, Sims' father lived to see his son reach the pinnacle.

Sims read medicine irregularly with Dr. Churchill Jones during 1833 and 1834, had one term of four months at Charleston Medical College, South Carolina, November, '33, to February, '34, and then seven months, November, '34, to May, '35, at Jefferson Medical College in Philadelphia. Here he learned anatomy, surgery, and the symptoms and therapy of diseases but never had the opportunity to treat a patient.

He began practice in Lancaster, South Carolina. His first two patients were infants, both of whom died of cholera infantum. Sims was so crushed that he resolved to leave the community and go as far away as possible.

His father and he traveled by buggy for three weeks to get to Mt. Meigs, Alabama, where Sims began again. In November, 1835, he bought the practice of Dr. Childers with a note for \$200.00. It was here in December that he diagnosed a huge liver abscess, which had been overlooked by all the older physicians, won the dying patient's consent to operate, and the man recovered.

The fame of this achievement gave Sims a great reputation, a livelihood, and, more important, a following large enough to enable him to develop his surgical skill. It is interesting to contemplate how often a real start in the practice of medicine is based on a single successful result, regardless of its scientific or technical significance. Witness the emergency tracheotomy performed by Dr. W. T. Bull in a New York restaurant, which sent his name and fame reverberating around the country. And by the same token how pathetically often has a really competent physician died in obscurity for lack of opportunity.

During 1836, Sims had his first and almost fatal attack of malaria. He believed his life was saved by an English druggist of Montgomery, named Thomas B. Coster, who was out on a collecting excursion. Coster filled Sims with quinine and brandy and stayed with him until he recovered.

In June, 1836, Sims joined a company of militia to stand off the Creek Indians until the regulars came. There was no fighting but Sims became acquainted with 120 young men of the best families in Montgomery, Alabama. These contacts stood him in good stead when he eventually moved to this city.

In December, 1836, Sims finally won his bride, brought her to Mt. Meigs, and soon thereafter to a spot ten miles away called Cubahatchee.

At this time in Sims' career he had no particular interest in his profession except as a livelihood. He was prepared to take up anything that might offer an "inducement of fortune." This was the time he accepted an offer to be set up as a clothing merchant in Vicksburg, Mississippi. Fortunately for womankind, the Philadelphia capitalist backed out. Practice flourished and Sims led an easy and carefree life. He hunted as he rode the countryside and yet earned \$3,000.00 per year.

Then, in July, 1840, the malaria which was endemic throughout that region struck him again, and also his wife, children, and slaves. This determined him to get away from the swamplands and so he settled in Montgomery. During his first year there he had seventeen attacks of malaria. After two years he was in fair health and his great surgical skill soon gave him the largest following in the entire area. Clubfoot, strabismus, harelip, amputations, all responded to his skill.

His first publication, on the repair of a frightful harelip, was literally thrust upon him. Throughout Sims' school days he was unable to write compositions. He graduated from Columbia College only because a classmate wrote two required essays and signed Sims' name with his knowledge. Incidentally, this is the only recorded evidence that Sims ever deviated, however slightly, from the path of honor. Dr. Harris, founder of the Philadelphia Dental College, saw the dental cast in Sims' office and insisted that Sims write up the case for the *Journal of Dental Surgery*. Then Sims hid the journal among his books where his cultured and literary friend, Dr. Ames, found it. Dr. Ames' unstinted praise, coupled with his own lament at his inability to write well, gave Sims the reassurance which enabled him to continue his case reports.

Sims' views on trismus nascientium, his autopsy reports, his belief that the cure of intracranial hemorrhage in the newborn due to overriding skull bones could be achieved by lateral posture caused him to label this observation as his first great discovery in medicine. He derived much satisfaction from the fact that his theory and treatment were substantiated by a publication thirty years later concerning a dozen infants who had this trismus and had been saved by his method of treatment.

Sims, now thirty-two years old, was firmly established as a leader in a flourishing community. He discarded his gun, concentrated on his practice, had a good home, an increasing family, and a wonderful and understanding wife. On their premises he had a cabin in which he kept his Negro patients. For ten years he had ignored obstetrics and gynecology. This was 1845.

Now Fate, in the guise of a sleeping hog, stepped in to overthrow this picture of serenity. This hog roused with a grunt. Fat Mrs. Merrill's startled pony sprang from under her, and she sustained a painful, impacted retrodisplacement. Sims who was making house rounds responded to the emergency call. Mrs. Merrill was suffering intensely. Sims reluctantly did a vaginal examination. He made the diagnosis. Recalling the advice of Prof. Prioleau of Charleston Medical College to apply pressure per vaginam and per rectum with the patient in the knee-chest position, Sims tried this maneuver, omitting the rectal phase which was even more repugnant to him than the vaginal examination. Fortunately the Merrill vagina admitted more than one finger. The impaction yielded, the lady experienced immediate relief, and then great mortification as she turned on her side and heard the garrulity of her vulva. Sims' stilted and formal explanation to her of the true source of this explosion makes delightful reading.

It was at this point in time that the flash of genius hit his mind and went on to spread its beneficence around the world. Sims had just seen three hopeless

slave victims of vesicovaginal fistula, the first he had seen in ten years of practice. The first was Anarcha, aged seventeen, whose seventy-two hour labor he had been called upon to terminate. The others were Betsy and Lucy. It should be noted that Anarcha likewise had a large rectovaginal fistula. The eventual cure of this defect must be taken for granted since nowhere have I found a description of its repair. That Sims did cure these posterior defects with equal facility is demonstrated by the fact that he cured such a patient in New York before his first case of vesicovaginal fistula was made available to him. Now he connected Mrs. Merrill's ballooning vagina with the possibility of visualizing and repairing these fistulas. He was familiar with the almost routine surgical failures and the very few successes recorded in the literature. He was sure he had the solution. Ignoring his long list of house calls, he bought the now famous pewter spoon, gathered up his two medical students, hastened to his little hospital, and examined Betsy, whom he was sending home that day untreated. Visualization of that huge fistula gave this skillful surgeon a thrill of imminent victory over a loathsome condition, this lifetime of wretchedness which had cursed womankind through all the ages.

Sims spent three months preparing his instrumentarium. Then in December, 1845, in the presence of the local fraternity, he operated upon Lucy. He pared the edges, sewed with interrupted silk, and drained the bladder with a sponge strip in the urethra. Lucy almost died of sepsis before Sims removed the foul sponge and decided that a permanent catheter was the answer. The fistula was smaller but not closed.

Sims had enlarged his hospital to a two-story shack of sixteen beds and scoured the countryside for cases. Henceforth for four long years Sims persisted. He carried the expense of feeding and housing these slaves while their owners paid the taxes and clothed them. No patient died and no patient was cured. Sims' brother-in-law, Dr. Rush Jones, wrote, pleading with him to stop, spare his health, and give his full time to his practice. Sims' reply reveals his intensity of purpose and his semireligious fervor.

"My dear brother, if I live I am bound to succeed; and I am as sure that I shall carry this thing through to success as I am that I now live, or as sure as I can be of anything. I have done too much already, and I am too near the accomplishment of the work to give it up now. My patients are all perfectly satisfied with what I am doing for them. I cannot depend on the doctors, and so I have trained them to assist me in the operations. I am going on with this series of experiments to the end. It matters not what it costs, if it costs me my life. For, if I should fail, I believe somebody would be raised up to take the work where I lay it down and carry it on to successful issue."

His colleagues who had assisted him had long since lost interest so Sims trained his patients to act as his assistants.

Then, in 1849, Sims tried perforated lead shot to hold his silk sutures, while re-operating upon Lucy. Again it failed. Lead sutures also had failed. Sims was certain of his technique and was now convinced that his failures were due to the suture material. The bit of discarded brass suspender wire lying in his yard inspired him to have his jeweler make up some pure silver wire.

Anarcha was next in line. Sims used four silver sutures threaded through lead strips on each side and held by lead shot. The postoperative course was strikingly different, with no cystitis, no urethritis, and with complete comfort. Removal of the silver wire in the "Sims" position revealed complete healing. Thus in June, 1849, Sims achieved his first complete cure of vesicovaginal fistula. This was the thirtieth operation on Anarcha. Promptly thereafter he cured the entire group in his hospital. He was sure now that he had made an important discovery.

It is thrilling to read any one of the innumerable references and abstracts which recite the story of this revolutionary surgical achievement. But that is as nothing compared with the fascinating complete original article as Sims wrote it. Only there does one begin to grasp the magnitude of his labors. He presents a most comprehensive survey of the futile efforts of the world's greatest operators, properly pointing out that the occasional successes were accidental. He gives in detail his own endless struggles and then sets forth his three claims for originality:

"1st, For the discovery of a method by which the vagina can be thoroughly explored and the operation easily performed.

"2nd, For the introduction of a new suture apparatus, which lies imbedded in the tissues for an indefinite period without danger of cutting its way out, as do silk ligatures.

"3rd, For the invention of a self-retaining catheter, which can be worn with the greatest comfort by the patient during the whole process of treatment."

In my humble opinion, a reading of this original article in its entirety should be a "must" for every young physician who aspires to recognition in the field of gynecology and obstetrics. Whoever does this cannot fail to recognize the importance of a comprehensive knowledge of the literature and the need for patience and persistence in any type of research. Too many young men are too prone to nibble at research while strenuously cultivating a following. The story of Sims' years of devotion and sacrifice should be an everlasting inspiration.

Meanwhile sorrow through illness and death had invaded his home. Sims' second son died in October, 1848, aged three, a victim of the diarrhea which was endemic in that area and in all age groups, and inevitably fatal. Then Sims developed the diarrhea and collapsed six weeks after his successes with the wretched victims of vesicovaginal fistula. He and his wife tried New York for three months. He grew worse. He was emaciated and was looked upon as a dying man. Actually he weighed less than 90 pounds at this time. Sims survived by going to Coopers Well, Mississippi, in January, '50, where in twenty-seven days he gained twenty-seven pounds. Curiously, he had to borrow \$200.00 to enable him, his wife, and two daughters to make the trip—this after ten years of a flourishing practice. The explanation may be that this was cotton country. All transactions were on credit until New Year's. After the crop was sold there was a settlement of all debts.

For the next six years (1849-1855) Sims had recurrent debilitating attacks of chronic diarrhea. In 1851 and '52 he was prostrated repeatedly and awaiting

death. It was then from his bed in Philadelphia that he wrote his article on the cure of vesicovaginal fistula as a last offering to the world. It was published in the *American Journal of Medical Sciences* in January, 1852. It occupied 23 pages and had 22 wood cuts.

Finally, in February, 1853, again prostrate in Montgomery, Sims realized that his only hope of survival was to move permanently to New York City where he had usually improved. He sold his interest in a drug store to his partners, Drs. Jones and Baldwin, for \$7,500 in notes payable in twelve months, and his home for \$10,000 on credit. His wife together with the younger children remained in Montgomery long enough to dispose of their holdings and to place their slaves in positions in which they could earn their redemption money payable to Sims.

In New York, Sims bought a house at 89 Madison Avenue for \$15,000, with \$5,000 down and used the remaining \$2,500 for furnishings. He now had a mortgaged home, \$1,000 in cash, no friends, no influence, no health, and nothing to recommend him except his article on vesicovaginal fistula published one and one-half years ago.

In the following months Sims met the leading surgeons of New York. Dr. Buck used him to repair a third-degree perineal laceration. Dr. Mott sent him a case of vesicovaginal fistula which Sims promptly cured. This was the first patient cured in New York City (Autumn, 1853). Thereafter the procedure became common property and was employed by the surgeons of New York without any further recognition of Sims' existence, excepting always that by Dr. John W. Francis.

What a commentary on our profession! An article published in a leading medical journal, a proven procedure for the cure of a hitherto incurable affliction, set forth in the most complete detail, with numerous (22) illustrations of the newly devised instruments and sutures, the successive steps of the operation, the preoperative and postoperative care, all in the clearest language, and what happened?

Not one of the surgeons anywhere in the large cities paid the slightest attention to the article. Two years passed before Sims himself could demonstrate his operation in New York. Then, presto, everyone took over and Sims was ignored.

Perhaps one can understand the complete disregard for Sims' publication. After all who was Sims? A country surgeon with no professional background or connections, claiming to cure a condition which was not curable in the hands of the leading surgeons of the world. Preposterous—why bother with it? What is more difficult to understand is the almost complete cabal among the great surgeons of New York which barred Sims everywhere and would have driven a weaker spirit into oblivion.

It was at this time that Sims conceived the idea of a Woman's Hospital. The leaders of the medical profession listened and rejected the idea for various reasons. Meanwhile the family cash was gone. They turned their home over to their first New York landlady who boarded them in lieu of her lease rental,

and filled the home with boarders. A year of misery, poverty, and ill health passed.

During these trying times Sims' letters to his wife and to his father reveal his strong religious faith and the strength of his will and determination. He attended religious services whenever and wherever he could, at home and abroad.

He wrote repeatedly about the sermons to which he had listened, sometimes critically but always with faith. Father H. C. Semple of Loyola University, New Orleans, who wrote a beautiful tribute to Sims in 1923 quotes the old Latin proverb, "Ubi tres medici ubi duo athei," and then goes on to show how completely Sims' life repudiated this calumny. Probably his most revealing profession of faith was in a letter written to his father on August 8, 1855, in which he compared their lives. In early life, he wrote, they were both mere moralists. Both had similar reverses of fortune and afflictions at about the same period in their careers. Sims beseeched his father to make a public declaration of faith. In fact, his father who fought for the Confederacy at the age of 73 did join the Methodist (not the Presbyterian) church after that war.

Again fate stepped in. Sims encountered a former patient now living in New York, a Mr. Beattie, to whom he told his story of exclusion from any responsible medical opportunity and his vain hope of getting a Woman's Hospital where he could work. Beattie introduced him to a newspaper reporter, Henri L. Stuart, and from that moment the tide began to turn. Stuart arranged for an invitation meeting of physicians to be held in Stuyvesant Hall in May, 1854. Stuart sent out 700 invitations. Then the day before the meeting Stuart took Sims to meet the editors of fifteen newspapers and had him tell his story to each one. Every paper published an item about the meeting, and the Hall holding 250 was filled in spite of a heavy rain. After this meeting a committee was organized in which Sims now played the dominant role. He selected the heads of the three Medical Colleges, Drs. Stevens, Mott, and Green, and Dr. Francis representing the obstetricians.

In the autumn Sims' guiding star, Mr. Stuart, persuaded him to organize a Woman's Board.

In December, 1854, Sims was making progress with his hospital movement but he was so poor he could put nothing in the children's Christmas stockings nor buy a new coat for himself to call on the ladies whose help he was seeking to get the hospital for women.

Yet this is part of what he wrote to his beloved wife: "I feel that a clear head and a good heart are much better than fine linen and fine clothes. It's good to be poor provided that poverty does not oppress and wholly crush us out. I am just poor enough to be stimulated to extraordinary efforts; yet I feel that if I were a little more distressed I could hardly bear it. God in his mercy has in my case most assuredly tempered the wind to the shorn lamb . . . When I pause to consider what I have done here and how it has been effected I cannot but acknowledge that an overruling Providence has wisely directed all things for the best."

Then this excerpt from a letter to his wife about visits to the great: "You know how I hate mere idle compliments, bowing and bobbing out; I would not go at all but I may have a chance to drop a good word somewhere for the ad-

vancement of the CAUSE, the cause of poor suffering woman. This is at the bottom of my breast, it is at the top of my throat, it fills my brain. It is the grand moral object of my professional life—next to you and my children stands in my affection the success of this glorious mission. When I look into my heart I do not see that my motives are at all selfish—you can understand me, the world may not. It is a glorious thing to feel that you are above the dross and glitter of mere pageantry. Money is trash and may be blown away by the wind. Honors are evanescent and may be snatched by another. Even reputation may be tarnished by the slanderous tongue of an envious villain. But the proud consciousness of rectitude coupled with true benevolence lives in the heart of its possessor and is as immortal as the soul itself."

By February, '55, Sims had accomplished his purpose. The hospital was organized February 10, 1855, and actually opened May 1, 1855, at 83 Madison Avenue. At the dedication of this temporary hospital Dr. Valentine Mott, perhaps the greatest surgeon of his day, who had learned Sims' techniques and then dropped him, spoke as follows: "Go on, Dr. Sims, in your work of charity and benevolence. Although no marble urn or inanimate bust may tell of your honor and renown you will yet have in all coming time a more enduring monument, and that monument will be the gratitude of woman."

Thus gracefully did Dr. Mott assign all charity patients to Sims. He lived long enough to see Sims become the master gynecologist, not only in New York but throughout the world.

The hospital site at 83 Madison Avenue in New York City, a few doors from Sims' home, was selected to save his strength. Sims was again suffering from his recurrent diarrhea. However, he was able to operate at least once daily. The beds were filled at once; all were charity patients. After six months Sims got permission to appoint an assistant. He offered the post to Dr. Frank Johnson, Jr., and then to Dr. George F. Shrady. Both men were being married and both declined. Dr. Thomas Addis Emmet of New York had just married a Southern girl whom Sims had known since childhood. And thus opportunity came to Dr. Emmet.

The Woman's Hospital had no friends among the leaders in the other hospitals. Sims was called a quack and a humbug and the hospital pronounced a fraud. But the work went on and physicians from everywhere came to see the new operations. Sims' private practice grew much faster than his poor health could stand but his poverty finally was at an end.

Then came the plans for the Woman's Hospital of the State of New York. The charter was obtained in 1857 and titles to the land in April, '58. The location was the old Potter's Field and the city relinquished its title to the land in exchange for fifty free beds in perpetuity. Sims opposed the block style plan of the building. He wanted a pavilion system but did not have his way. So in June, '61, he went abroad to study hospital structures. When he returned in 1862 the first architect had died. The new architect agreed entirely with Sims' ideas.

You may recall that the War Between the States began in April, 1861. Sims sailed for the British Isles in June, 1861. He described his feelings toward the conflict as a struggle between his intense love of the South and his complete

professional orientation toward the North and especially toward New York City and the Woman's Hospital. His feelings are set forth in a letter to his wife in New York, written in Paris, November 1, 1861.

"The unfortunate state of political affairs at home places us in a very precarious position. I feel that we are not worth one dollar today. Let us do as we always have done, accept our position as we find it, and look continually to Him who overrules all things for the best. Financially the war ruins us. I have nothing but wife, children, health, reputation, and plenty of labor. So far a man is blessed. I am content, nay happy, and truly thankful that I am so well off. Our property in New York is valueless to us, and will soon be worth nothing. Our property at the South yields nothing, and may all be lost under the sequestration act. If we remain in New York, the probabilities are that it will all go into the Confederate treasury. If we take the oath of allegiance to the Northern States, it is absolutely certain to be confiscated, and I will be worse off pecuniarily but better off professionally. I am just as well satisfied, just as cheerful and happy, as I can be under the circumstances. You know I always have a happy faculty of accommodating myself to any position in which I may be placed. I wish you to go and see Mr. Simeon Draper, and tell him that I came over here to remain six weeks; that the Government, since then, requires every American citizen to get a passport and to take the oath. Tell him that my father and all my family are rebels, that they are fighting for the Confederate government, and that I sympathize with them; that if I did not I would be, as a man, totally unworthy of the confidence that he and all the good people of New York have placed in me for the last eight years. That however much of the rebel I may be at heart, he knows very well that I am as incapable of doing a traitorous act, against the flag under which we live at the North, as a five-year-old child would be. My sentiments I cannot help, for I lived forty years of my life at the South. The companions of my youth are the leaders of the great Southern rebellion. My father, now seventy-three years of age, is one of its soldiers; our whole family are in arms; your father and mother, my mother, and one of our beloved children have graves on Southern soil, and how under heaven could we be otherwise than as we are, unless lost to all sense of humanity. Give this letter to Mr. Draper, to read, and after that, if he gives you his assurance that I shall not be subjected to any indignity or annoyance on my return home, let me know. If he hesitates one second, let me know it, and my resolution is taken. Somehow or other you have on one or more occasions been placed in the position of assuming great responsibilities in piloting our little lifeboat, and your presence of mind, your judgment, and your courage have always been equal to the emergency, and I have the most unbounded confidence in your wisdom. You are again placed in that trying position; and now, under all the circumstances, I ask you this question and leave it to your decision: Do you think it would be wise for us to remain in Europe until the war is over? Think of this and write me your decision, and what you say that will I do. If our two furnished houses could be rented for enough to pay off their mortgage, interest, taxes, etc., and leave something over, it would be better than living in them, for here we can live in a cottage in the suburbs of Paris for very little, while I could give my time to the preparation and publication of my works, which the world outside of the Woman's Hospital is sadly in need of. I would have some time to devote to you and the children, and really I don't think the change would be a very unhappy one. Is it not strange to hear one speak so calmly about such a sad reverse of fortune? I suppose if I were put in Fort Lafayette I would make a virtue of necessity, and turn it all to the best account. But, if we go into voluntary exile here, it would not be an exile of want or destitution by any means. Turn me loose today anywhere in Europe, and I shall be able to support you all in a modest and unpretentious style. I feel that I have now equally as much influence in Europe as in my own country. You cannot imagine what an interest I have created here by my professional labors; and in six weeks from this I could sit down anywhere and draw patients in abundance. This grows out of the fact Paris is like New York. It is

to Europe what New York is to our whole country. One of my friends and counselors said to me yesterday that my Parisian baptism is my salvation in Europe. I have already operated four times, and in all cases successfully. I operated today for Velpeau, at La Charité. It was a great occasion. Many distinguished men were present, and a large class of students. The case had been previously operated on about seventeen times by Joubard de Lamballe. Velpeau, Malpaigne and Denonvilliers were perfectly delighted. After the operation, I said if the young men wished it I would make any explanations or answer any questions they might ask. I was too modest to say I would deliver a lecture. The young men took their seats, and Velpeau, Malpaigne, Denonvilliers, Trélot, and a host of other old fellows sat by me. As I talked, Mr. Souchon, a medical student from New Orleans, a student of Professor Stone's, sat by and translated as I spoke, and everybody seemed perfectly satisfied with his rendering of the subject. I never saw such complete satisfaction in all my life. Malpaigne, who is nicknamed the 'Barking Dog' because he snarls and growls at everybody, sat there patiently all the time, occasionally asking a question on some point that he did not comprehend, and when he left he shook my hand, and thanked me cordially over and over again, and everybody said that he was never known to speak well of any one, or to any one in a familiar way before. They consider my triumph over him as an era in surgical polemics. Colonel Robert E. Cox was there, and he says the lecture was one of the best that he ever heard. That grows out of the fact that a man cannot afford to say a silly thing, or to waste words, when they are to be rendered in another language."

Sims, the victim of such divided loyalties and with a financial stake in Montgomery, Alabama, as well as in New York, decided, rightly or wrongly, to avoid a commitment.

His heart, his family ties, his affections were all in the South. His loyalty as an American citizen lay with the North. He was convinced that the Southern states had every legal and moral right to secede. He was equally convinced that secession would be an accomplished fact in a matter of months. Meanwhile the support and welfare of his considerable family held top priority in his thinking. He believed that active participation with either side spelled financial ruin. His solution was neutrality. This man was neither a moral nor a physical coward as was revealed by his whole life. He was not concerned with self-preservation. Censure for his decision in the face of his recorded conflicting emotions does not seem warranted.

On this first trip to Europe, Sims was welcomed as a master surgeon in every city he visited. And everywhere he demonstrated his operative skill and technique.

His hero before sailing had been Simpson of Edinburgh who had published much in the young specialty. When he saw Simpson do his cervicectomy for dysmenorrhea he was disillusioned. Moreover, Simpson claimed never to have had an accident. When Sims related his own accidents to the leaders in Aberdeen, Dublin, and even Edinburgh, they laughed at his credulity. They cited the deaths Simpson had had and so Sims uncrowned his hero.

He extolled Syme as the most brilliant diagnostician and operator he ever encountered. Of course Syme had acquired his rapidity and skill in the pre-anesthetic era.

It was on this trip that Sims lost his first patient after repair of a vesico-vaginal fistula. This was in the Samaritan Hospital of London. The autopsy revealed that both ureters had been ligated.

In Paris, Sims cured five patients, each under different auspices, and in a month he had won the admiration of the entire profession.

In Brussels, Sims performed three operations in one morning. One patient died a week later. Autopsy revealed that the catheter had perforated the bladder. Sims assigned this to the nurse who was unskilled in the handling of a permanent catheter.

Sims returned to New York in January, 1862, to find his country in the very midst of a great civil war. He was so unhappy at this state of affairs that he took his family to Paris in July of that year. He intended returning each autumn for six months to earn the money to maintain his family abroad. He found, however, that his services were in such demand that income was no longer a problem. He was still convinced that the war would end soon with secession accomplished.

During his summer at Baden Baden in 1863, Sims compiled his *Clinical Notes on Uterine Surgery*. It was published in London in 1866 and represents his only text. Actually it is a series of case reports given in minute detail, and for a long time was a revolutionary and authoritative volume. Reading of any single report would serve to show Sims' scientific bent, his wide interests, knowledge of the literature, and his careful case notes.

In the two years preceding his departure for Europe in 1861 he treated ten patients for long-standing primary sterility. In every instance the husband's semen was normal. Each patient had some type of endocervical disease which Sims treated. Then he performed artificial insemination fifty-five times, using the semen from the posterior fornix. He started with three drops, using a syringe which he devised. Penetration of the canal was stopped mechanically at $1 \frac{1}{16}$ inches. The syringe permitted injection by half drops. Sims decreased the dose to one-half drop. He was meticulous about maintaining the syringe at body temperature. His final patient, sterile for nine years, became pregnant but miscarried after a fall at four months. Sims discarded all but twenty-seven of the inseminations because of faulty technique. So he stated that he had achieved his one and only success in twenty-seven trials. Sims found that the spermatozoa died in a few hours in the vagina, but lived at least forty-eight hours in the cervix. A. Martin, at a centenary celebration of Sims' birth, 1913, gave Sims credit for the first successful artificial insemination in the human being. Martin who knew Sims said, "He remained always a simple, modest, lovable man."

Sims and his family remained abroad until 1868. He moved from Paris to London in 1866, expecting to return to the United States shortly. His return was postponed by the endless demands for his services both in London and on the continent.

In New York his practice flourished at once. He continued to devote his talents to rich and poor alike until 1870 when he returned to Europe for another tour of operating.

After success came to Sims he wore the conventional black Prince Albert coat buttoned to the chin like the French surgeons, and like them kept his right

hand in the breast and saluted by languidly throwing out his left hand. This was not affectation but a protective mannerism. Once in Texas where he was called to operate, an enthusiastic Texas admirer crushed his hand and almost shook his arm off.

Sims' mild manner and gentle nature were extolled by all his friends. Yet he was quick to repulse attacks on the soundness and originality of his procedure and the armamentarium by which he had made vesicovaginal fistula curable. Concerning one objection he wrote:

"It has been objected to this speculum that its use requires the assistance of a third person. Apart from its real value there could be no stronger reason for its universal adoption. I insist that a third person should always be present on such occasions. Delicacy and propriety require it and public opinion ought to demand it. I am sure that I have never made a vaginal examination or used a speculum a dozen times in my life without the presence of a third person. . . . We can never make a mistake if we always cultivate the same gentleness and kindness toward the poorest hospital patient that we would use toward the highest princess."

During this visit to Europe in 1871, the Franco-Prussian War broke out. Sims was in Paris where he promptly organized the Anglo-American Ambulance Corps and was made its surgeon-in-chief. He had a 400-bed hospital in which he worked for a month during the battle of Sedan, and where he acquired an intimate knowledge of gunshot wounds. Subsequently, in 1881, he published his views on the *Treatment of Gunshot Wounds of the Abdomen in Relation to Modern Peritoneal Surgery*. He addressed the New York Academy of Medicine on the same topic. The principles he laid down were obvious to him, the man of genius and vision. They were rejected completely by the leading surgeons in New York.

President James A. Garfield was shot in the abdomen on July 2, 1881. Sims who was residing in Paris was consulted for his opinion as to the proper treatment. The accepted treatment was opium and poultices although some surgeons had ventured to invade the abdominal cavity and suture the bowel. Sims cabled: "If the President has recovered from the shock and if there is undoubted evidence that the ball has traversed the peritoneal cavity, his only safety is in opening the abdomen, clearing out the peritoneal cavity, tying blood-vessels, suturing wounded intestine and treating the case as we would after ovariotomy, using drainage or not as circumstances require."

His advice was rejected by the surgeons in charge. It was not until the great surgeon, W. T. Bull, adopted the open treatment in 1885, two years after Sims' death, that surgeons generally accepted Sims' views.

Here again was a perfect and pathetic illustration of the conservatism of an educated and enlightened group of men, dedicated to the service of humanity and yet resisting that which was foreign to their training and teaching.

To those who deplore and even deride the resistance of physicians to much that is new and untried, let it be said that physicians deal with and are responsible for the one irreplaceable commodity, namely, human life. Charlatans, quacks, and cultists have no reputation to lose. The safety of the population as a whole lies in this slowness of the medical profession to adopt debatable ad-

vances. The open-mindedness of our profession is evidenced sufficiently by its prompt adoption of diagnostic methods and therapeutic procedures and drugs which are manifestly sound. Of this there are endless examples.

Sims made repeated trips to Europe. During a crossing in July, 1871, he was called upon to give a Fourth of July address. It gave him an opportunity to set forth his views on the War Between the States and the postwar behavior of the North toward the South.

"It was said this morning, by my friend Mr. Train, the eloquent orator of the day, that the Fourth of July was annulled by the bombardment of Fort Sumter. Sir, the thunders of Fort Sumter were but the premonitory throes of a labor that ended in the new birth of one of the mightiest nations of the earth, for we can now truly say that we have been born again. If you applaud so vociferously this sentiment from a citizen of New York, let me tell you that it is from the heart of a red southerner, for I was born in South Carolina, was wholly educated there, and lived there till I was a full-grown man; that I was contemporary with Davis, and Stevens, and Toombs; that my political teachers were Thomas Cooper and Turnbull, Mr. Duffie and the immortal Calhoun; that I was for many years an intimate personal as well as political friend of Yancey; that in later years I was in the kindest and most sympathetic relations with Mason and Slidell; and that I sympathized heart and soul with the South in what you miscall a rebellion.

"With this record, if I can hail and celebrate this day, as every American should, who here shall dare repudiate it? Rebellion, did I just now say? Why, sir, this term as applied to our late struggle is false. Our civil war was a real war between what had been sovereign and independent States; a war of principles and a war between political equals. From the very foundation of our Government, from the days of Jefferson, and Madison, and Hamilton, and Jay, we had incorporated into our Constitution two great antagonistic principles that have been continually threatening our existence as a nation. These principles have been variously interpreted by parties—on the one side representing the rights of the States, and jealous of the powers delegated by these to the Federal Government, and on the other by a party advocating a strong central Government, and ever ready to encroach upon the rights reserved to the States. These principles, thus underlying all parties, by whatever name called, have been at unceasing war ever since the adoption of our Constitution. We fought them out on the tariff; we fought them out on the bank question; we fought them out on internal improvements; we fought them out on the territorial questions; and on a variety of side issues.

"And in our great civil war these questions of the rights of States, and of the power and authority of the central Government, were the real questions of the day, all others being incidental and subsidiary. While they were general and theoretical all was well. But as soon as they became sectional and practical all was lost. The Southern States, standing upon their reserved rights, seceded and formed a new federation, and thus the States under the new and the old federations fought out in the field the old principles so often contended for in the legislative halls, and we of the South were beaten here as we had always been before. And, strange as it may seem, in this great struggle for national existence, the country did not produce a single man, North or South, who rose to the dignity of true statesmanship. Not one man who grasped the whole subject in all its bearings and issues. Why, sir, every movement at the North was one of temporary expediency, every step at the South one of utter desperation. North and South were alike blind and mad. Each equally sowed the wind, and each alike reaped the whirlwind. But God Almighty rode in the tempest and directed the storm, and its result was according to His will. The questions at issue were too mighty for the puny intellect, but He in His wisdom decided and overruled all, and they were settled in a way not foreseen by any. And now, sir, under these circumstances, what is our duty to ourselves and to our country? We now have a Government that is no longer a rope of sand, one that is

felt to be a real power, not only at home, but a leading power among the nations of the earth. I am proud of my country abroad, but ashamed of it at home. The humiliation of the South is inexcusable. Its ruin is unjustifiable. But, notwithstanding all this, when I calmly survey the past, when I closely inspect the present, and when I look into the depths of the future, I must in all sincerity say that I now think the worst thing that could have happened for the country at large would have been the success of the cause to which my heart and soul were honestly and earnestly given, and conversely, that the best thing that could have happened under the circumstances for the cause of civil liberty, not only in our own country, but throughout the civilized world, was the success of the principles based upon a strong central Government.'

The great professional tragedy in Sims' life came about in 1874. For many years Sims had sought unsuccessfully to induce the Ladies' Board of the Woman's Hospital to consent to the admission of cancer patients. Then in 1874 the ladies ruled that Sims could have no more than fifteen visitors at any operation. The Board of Governors and three of Sims' colleagues, including Dr. Emmet, supported the Ladies' Board.

Sims refused to accept this final interference with his freedom of action. He knew his ability as an operator and as a teacher. The greatest physicians of the world had paid him homage. His devotion to the ills of womankind was his life's theme. He could not and did not accept such stupid attempts to hamper his work and his teaching. He resigned from the staff of the hospital which was truly his brain child and his resignation was accepted.

All of us know the crosscurrents which influence hospital boards. It is quite conceivable that this action had its background, in part at least, in the jealousy of Sims which existed among the leaders in New York and even in his own hospital. That the American medical profession felt quite differently was demonstrated promptly.

The following year Sims was elected unanimously to the presidency of the American Medical Association and served in 1876. The title of his address was "Legislation and Contagious Diseases." Moreover, in 1880, he was elected president of the American Gynecological Society. On that occasion his subject matter covered a survey of the progress which had been made in gynecology and obstetrics.

Nothing could undermine Sims' wide professional interest and zeal. In June, 1878, he published "Remarks on Cholecystotomy" quite independently of Bobbs of Indianapolis whose article, describing the first such operation, preceded Sims' by ten years. In December, 1878, Sims wrote on the "Extraction of Foreign Bodies From the Ear" and in March, 1883, he wrote on "Treatment of Syphilis." Altogether Sims published over eighty articles, many of them case reports, besides his *Notes on Uterine Surgery* and his *Story of My Life*.

After Sims resigned from the Woman's Hospital he spent more and more time abroad, usually in Paris. His assistant and successor, Dr. Thomas Addis Emmet, was extremely capable and entirely competent to carry on the fine tradition and high attainment established by Sims.

In this connection it is interesting to note how the jealousy and selfishness of many in the profession, which kept him an outcast in his early years in New York, persisted and cropped out long after Sims died.

The New York Obstetrical Society held its semicentennial meeting February 14, 1913, President George Gray Ward, Jr., presiding. The meeting was devoted to eulogies of the great men in the past history of the Society. Clement Cleveland gave the eulogy on Sims. He used all the glowing terms which Sims' genius and devotion warranted. Many other sketches were read. Then J. Riddle Goffe, eulogizing Thomas Addis Emmet, said: "Sims and Emmet became intimate friends and professional co-workers. Emmet helped to establish the Woman's Hospital. Dr. Sims was a great genius; he looked into the future, suggested new ideas, he was full of ideas. Dr. Emmet accepted him as his instructor but Dr. Emmet was the man who did the work. Dr. Sims did not have the patience to become a first-class operator, his technic was not of the highest order. Dr. Emmet was the man who looked into the details and worked out the problems."

Contrast this with the record of Sims' achievements in general surgery in Montgomery; his matchless skill in the correction of the most frightful cases of harelip; his innumerable cures of strabismus; his dogged perseverance for four years in his struggle to cure vesicovaginal fistula, at the cost of his health and practice; his painstaking creation of a completely new instrumentarium for vaginal plastic surgery which Emmet used unaltered; and, above all, the verdict of the world's greatest operators epitomized in the words of Civiale of Paris who had just witnessed Sims' work: "I beg to render you my homage. You are a true surgeon. Such gentleness and firmness; such dexterity and skill, such judgment and courage I have never seen before combined in such exact proportions in any one man. What a great lithotriptist you would have made. Come and be my pupil."

In 1880, Sims was stricken with a severe double pleuropneumonia which undermined his health seriously, leaving him with cardiac symptoms which he felt sure would shorten his life. Like many physicians Sims was a difficult patient. He refused whiskey and objected violently to inhaling oxygen. He demanded morphine more often and in larger doses than his physician prescribed.

After his recovery he continued his trips to Paris where he still remained the outstanding operator. On his last visit to New York in 1883, when he was about to sail abroad again, he was persuaded to remain over to operate upon the wife of a prominent citizen of New York. The date was November 12 and the patient recovered completely. Sims, however, died in bed the following night, November 13, 1883, while pursuing his habit of jotting down some notes on a piece of cardboard. His death was painless and instantaneous. He was survived by his wife and seven children, among them a son, H. Marion Sims, who became a physician of note and who edited his father's autobiography.

W. O. Baldwin, a physician in Montgomery, Alabama, was an intimate of Sims from 1840 until the end. Baldwin's eulogy delivered in 1883 at a Memorial Meeting of the Medical and Surgical Society of Montgomery, and included in the appendix section of Sims' own *Story of My Life*, paints a clear and untouched picture of the personality of this great man. Baldwin called Sims the most winning and captivating man he had ever met. He witnessed Sims' first

operations for clubfoot and cross-eyes and states: "He was even at that day a remarkably neat operator and I think handled the knife with more grace and skill than any man I have ever known of his age He was a bold, fearless and dashing operator, and would undertake almost any case that another surgeon dare encounter His services were sought by all classes of people, and in all kinds of cases. He was frequently called into consultation with the oldest and most experienced physicians of the place. . . . He was immensely popular and greatly beloved so that he was a formidable rival to the best established physicians, and with all these facts it would not be greatly surprising if he did not always escape criticism. But when such things were carried to his ears they never made the slightest difference in his feelings or his deportment toward the authors of them but he would meet and pass them with the same kind word and pleasant smile which were always his custom."

Baldwin spoke this tribute: "Gynecology today would not deserve the name of a separate and cultivated science but for the light which Sims' speculum and the principles involved in it have thrown upon it. It has been to diseases of the womb what the printing press is to civilization, what the compass is to the mariner, what steam is to navigation, what the telescope is to astronomy and grander than the telescope because it was the work of one man. . . . Sims alone discovered and invented the speculum and like Minerva from the brain of Jupiter it sprang from his hands alone, full fledged and perfect when he gave it to the world."

Glorious words these, however inaccurate Baldwin's deductions. Of course the speculum was known for ages, of course metal sutures had been used before, and of course occasional victims of vesicovaginal fistula had been cured surgically by Hayward, Pancoast, and Mettauer in the United States, by Jobert of France and Gosset of England. Sims did devise his own instruments, he did introduce silver wire, he did show how to get exposure, and he did cure these patients *uniformly*. That was his magnificent achievement.

In Montgomery, Sims took an active part in the formation of the Medical Society, and was one of the leading members in its affairs. He was from the first an assiduous student and thoroughly methodical in keeping notes, records, and histories of his cases, in reading medical journals, and in keeping up with the medical literature of his day. Quoting Baldwin again:

"True men often owe no little of their power and success to the hostility, jealousy, and littleness of others. He was not only a man of genius, but he was a lovable man, full of personal magnetism, full of kind and tender instincts, alive to the romance that redeems life from commonplace and routine, and abounding in those high impulses which make their subjects benefactors because they are enthusiasts in the pursuit of truth. No man could be an hour with him and not feel the simplicity and fervor of his nature, the straightforwardness of purpose and intent which went into all his intercourse with others, and the absorption of his whole being in the work he had set himself to accomplish."

Sims fulfills Sir John Bell's ideal of the qualities in a truly great surgeon: "The brain of an Apollo, the heart of a lion, the eye of an eagle and the hand of a woman."

H. A. Royster, in 1922, in writing of Sims stated that he had all the "Attributes of Genius":

1. To take infinite pains.
2. To develop the capacity for hard work.
3. To keep everlastingly at it.
4. To do one thing well.
5. Not merely to win success but to deserve it.

A résumé of the life story of this man reveals his nobility of character: his devotion to parents, wife, and children; his innate modesty and chivalry; his insistence on the presence of a third person whenever he examined a woman; his scrupulous financial integrity, and his extreme generosity; his incredible courage and tenacity of purpose, in the face of constant debilitating disease, first during the four years of trial and error before he cured a vesicovaginal fistula, and again in New York when he starved and almost died, was ignored and then vilified, and still fought to get his hospital; all this not for gain but to bring relief to a hopeless segment of womankind. Fellows and guests, this was a man.

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HYPERPLASIA AND HYPERTROPHY OF THE UTERINE VESSELS DURING VARIOUS STAGES OF PREGNANCY*

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of Medicine)*

FOR a good many years, the enlargement of the uterine wall during pregnancy was considered chiefly due to the increased size of the individual muscle cell. Illustrations to show this change in size appeared in all prominent textbooks. It was also well known that the uterine circulation increased considerably in size throughout pregnancy, the chief increase being in the earlier half. It was considered that the increase in the number of individual muscle cells of the uterine wall was either entirely lacking or very moderate indeed. However, in later years, hyperplasia of the uterine muscle cells was thought also to help bring about the increase in size. The origin of these new muscle cells was not commented upon freely. Stieve, as late as 1929, was the first to approach the subject from the standpoint of origin of these hyperplastic cells. Williams states that according to the researches of Luschka and Veit the increase in the hyperplastic muscle cells of the uterine walls during pregnancy took place only during the first three or four months. Stieve, on the other hand, felt that the increase continued throughout pregnancy. We feel from our recent observations that the increase in the number of the cells takes place chiefly in the first half of the pregnancy and the tendency decreases gradually until the thirty-sixth week and during the last four weeks is almost entirely in abeyance. Williams in the first edition of his textbook (1903) discusses the subject as follows: "The enlargement of the uterus is due primarily to the hypertrophy of pre-existing muscle cells but also to the formation of new ones during the earlier months." He states that according to the research of Luschka and Veit the formation of new muscle fibers is limited to the first three or four months of pregnancy. With this is associated a marked development affecting the blood vessels, especially the veins in the neighborhood of the placental site which become converted into large spaces, the so-called placental sinuses. Stander, in his edition of Williams' textbook in 1945, concerning the same subject, makes statements similar to Williams' and in addition he mentions that Stieve believes that this increase in the number of cells takes place during the entire pregnancy. Stieve in an elaborate monograph which he published in 1929 contended that the new muscle cells did not arise from muscle cells themselves but were from other sources. He does not contend that these muscle cells develop from pre-existing muscle

*Presented at the Seventy-Third Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 11 to 13, 1950. In the absence of Dr. Schwarz because of illness, paper presented by Dr. T. K. Brown.

cells in the uterine wall, but rather mentions such cells as histiocytes, adventitial cells, lymphocytes and fibrocytes, which to us appear rather vague as a source of origin. He does not mention the possibility that the media of the blood-vessel walls could supply these new muscle cells nor that these new cells have any direct association with the blood vessels.

Our attention to the question of the hypertrophy and hyperplasia of the uterine vessels during pregnancy came about in a rather interesting way. We had been working previously on the question of the origin of myomas from the uterine blood vessels, noting in many instances that when there was no definite evidence of beginning myoma formation there was a rather exaggerated hyperplasia. Furthermore, in subsequent study of hyperplasia of the endometrium, the same rather striking picture presented itself; that is, marked hyperplasia of the cells of the media of the blood vessels characterized by numerous long and flat nuclei which were increased in staining reaction. We felt that these hyperplastic changes were due to combined stimulation of estrogen and progesterone and we were able to produce these changes promptly in the rabbit with estrogen alone but to a more considerable degree with injections of estrogen and progesterone combined. In our discussion of the subject, Hawker wondered what cellular changes took place in the uterine blood vessels during pregnancy. So we immediately looked at some specimens at hand and found the very interesting changes which we are reporting.

In our observation of the excessive hyperplasia of the vessels associated with hyperplasia of the endometrium, estrogen plus progesterone showed the more striking reaction. Considering that in pregnancy the corpus luteum reaches its highest state of development about the sixteenth week, one would expect that the hyperplastic process would be highest at this point which is actually the case. From the sixteenth week to the end of the pregnancy there is a gradual diminution of this hyperplastic process which goes hand in hand with the retrogression of the corpus luteum of pregnancy. The vessels themselves become denser in structure, that is, the cells become compressed, the nuclei more elongated and stained more deeply, and the veins gradually lose their hyperplastic wall and appear more or less as sacs near and at term. It is true that the placenta produces a corpus luteum-like progesterone but apparently this does not have the same synergistic effect with estrogen as the progesterone of the corpus luteum per se.

Fig. 1.—Normal nulliparous arteries, inner outer third of uterine wall, shown as normal control. Note the moderate thickness of the wall and moderate number of evenly distributed nuclei in it. Hematoxylin and eosin stain.

Fig. 2.—Same vessels as in Fig. 1, orcein-van Gieson stain. The artery to the left is slightly wider with the normal internal elastic membrane standing out clearly and showing the numerous fine elastic fibrils in the media. Veins have no precise distribution of elastic tissue, as in this case the amount is meager, a few fibrils in the media, slightly more pronounced in the periphery, which when exaggerated is referred to as an external elastic membrane.

Fig. 3.—Uterine wall, outer third in a primipara, eight weeks pregnant, showing striking increase in size of artery, with beginning hyperplasia of muscle cells in the inner media. Note changes especially near lower portion.

Fig. 4.—Same artery as Fig. 3, orcein-van Gieson stain, showing normal elastic tissue content of artery. Hyperplasia therefore in media of artery.

Fig. 1.

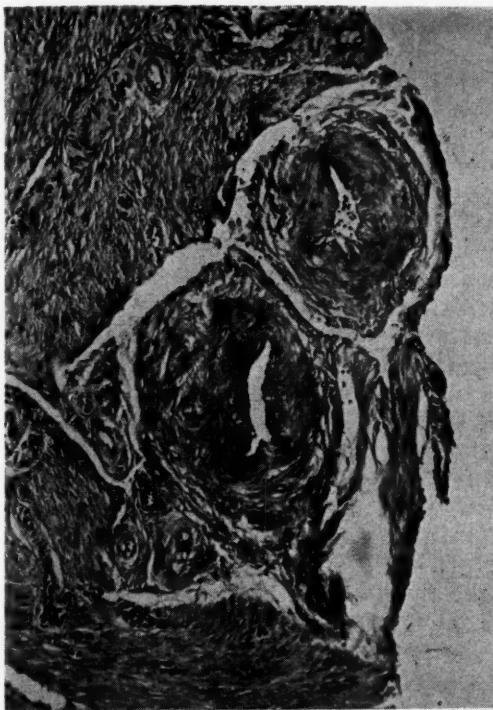


Fig. 2.

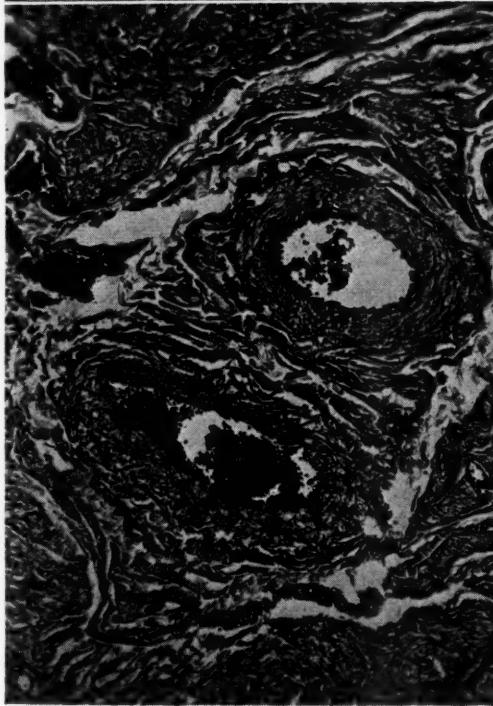
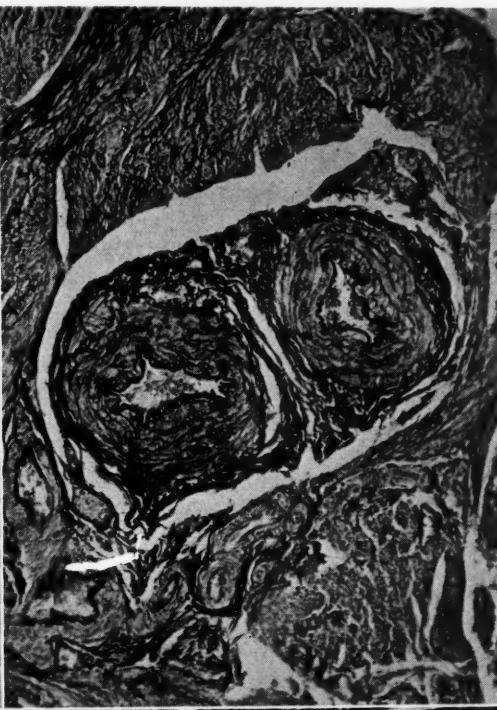


Fig. 3.

(For legends, see opposite page.)

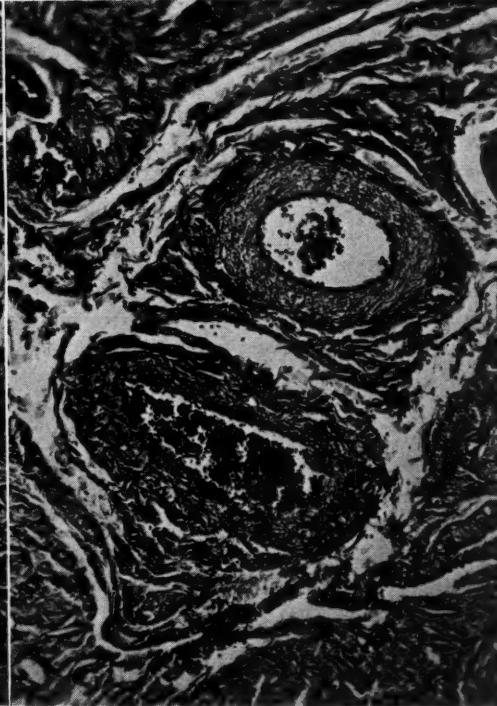


Fig. 4.

Material

The first section that we looked at was one of the uterine wall including the placental site, decidua, and myometrium and peritoneum. This section was from the uterus of the patient who was twelve weeks pregnant and who was gravida i. In other words, fifteen weeks before this patient's uterus was removed the vessels were those of a normal wall of a nonpregnant uterus. The increase in size in these vessels for the short period of twelve weeks was most striking. In this specimen, the arteries were extremely enlarged and the cells were so hyperplastic in appearance that they resembled uterine muscle cells at term. In developing this marked increase in size and number in these arteries, the cells were seen to disperse and lose themselves into the adjacent tissue. The veins were likewise affected and, when the section was shown to Dr. Willard M. Allen, he remarked that the condition was even more prominent in the veins than in the arteries and the amount of cellular dispersion appeared much clearer and more extensive. We were then determined to consult our files and study sections taken from pregnant uteri from the placental site to the peritoneum. We obtained some 45 specimens and divided them into three groups according to the trimester in which they fell. The hyperplastic condition described in the first group was continued until about the sixth month of pregnancy when there was a great tendency for the proliferation to diminish. In the arteries these cells were so large that they resembled the picture of full-term uterine muscle cells. Toward the end of the third trimester, these cells became flatter and more crowded together and the tendency to spread outward into the adjacent wall had practically been lost. The picture in the vein was quite different. The cells appeared as uterine muscle cells at term in the first trimester of pregnancy, but as term was approached they were thrown off to such an extent that most of the vein wall appeared more or less like a sac. This process continued until term when many veins, particularly at the placental site, were enlarged with dilated spaces and had practically no wall whatsoever. In other areas, later in the third trimester, a new vein wall had presented itself with flattened cells, not very thick, but still holding open a rather large lumen.

The interesting thing in connection with this hyperplasia is that it made no difference whether or not a primiparous uterus or a multiparous uterus was concerned, the hyperplastic activity appeared in both arteries and veins to the same degree. Further, even when, in the multiparous uteri, the vessels showed changes of marked subinvolution, they were capable of producing this hyperplasia as well. We feel from these observations that not only do the arteries and veins undergo this marked hyperplasia and hypertrophy during pregnancy but they supply the uterine wall with the new muscle cells. One need not go so far as Stieve has to explain the production of these new muscle cells on some rather odd development of cells such as he has mentioned. Our illustrations with rather detailed legends will bring all these points out clearly and we refer the reader to a careful study of them.

In presenting the illustrations, we felt that it was of the utmost importance to compare the physiologic hyperplastic changes in the uterine vessels in the pregnant uterus to the uterine vessels in the nonpregnant state.

Fig. 5.—Pregnant nulliparous uterus, eight weeks, showing section of entire vein with beginning hyperplasia of the muscle cells of the media.

Fig. 6.—Same field as Fig. 5, orcein-van Gieson stain, showing normal distribution of elastic tissue of vein.

Fig. 7.—Pregnant nulliparous uterus, eight weeks; large hyperplastic vein, inner third of uterus showing marked proliferation of the muscle cells of the media.

Fig. 8.—Artery, outer middle third of uterus, eight weeks pregnant, primiparous, showing marked pregnancy hyperplasia. Note especially the particularly large muscle cells as in late pregnancy. Note beginning tendency to invade adjacent tissue.

Fig. 5.



Fig. 6.



Fig. 7.

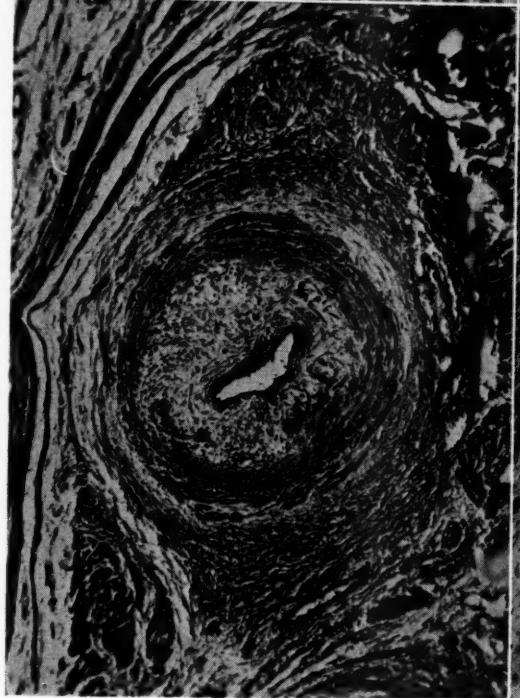


Fig. 8.



(For legends, see opposite page.)

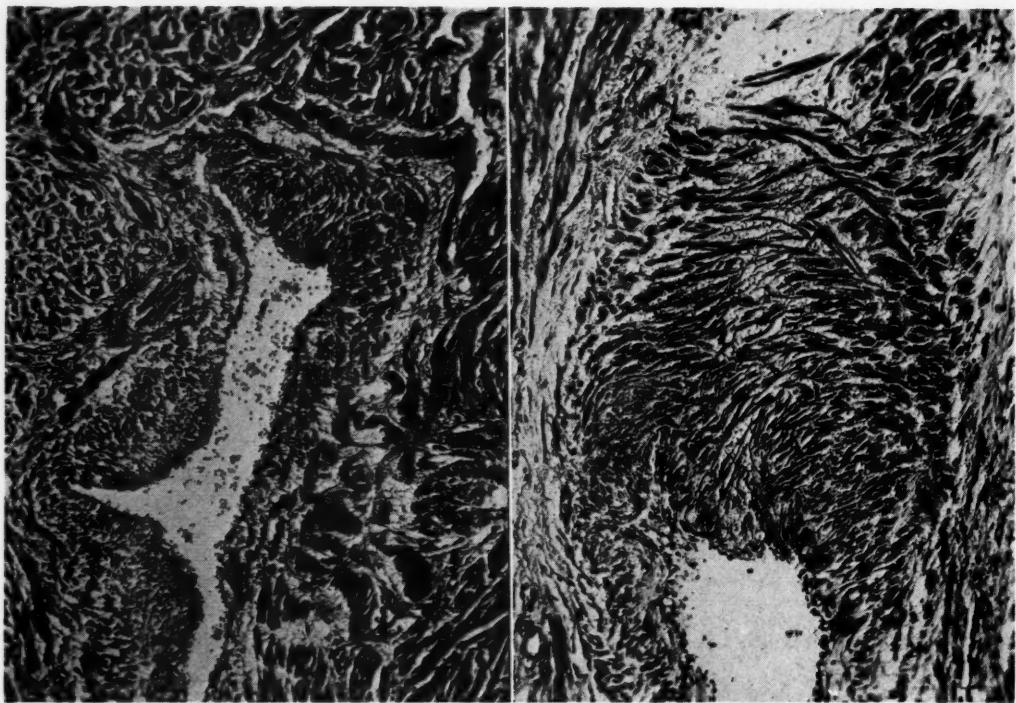


Fig. 9.

Fig. 10.

Fig. 9.—Pregnancy, twelve weeks, primiparous, outer middle third of uterus showing large hypertrophic and hyperplastic vein. Wall varies in thickness as a result of a more rapid penetration of the media muscle cells into adjacent uterine wall. This penetration by term leaves the vein almost sac- or sinuslike in character.

Fig. 10.—From same uterine wall as Fig. 9. Vein, hyperplasia. Note varied thickness of wall. At top of cells of the media look like muscle cells at term. Note the penetration into adjacent tissue.

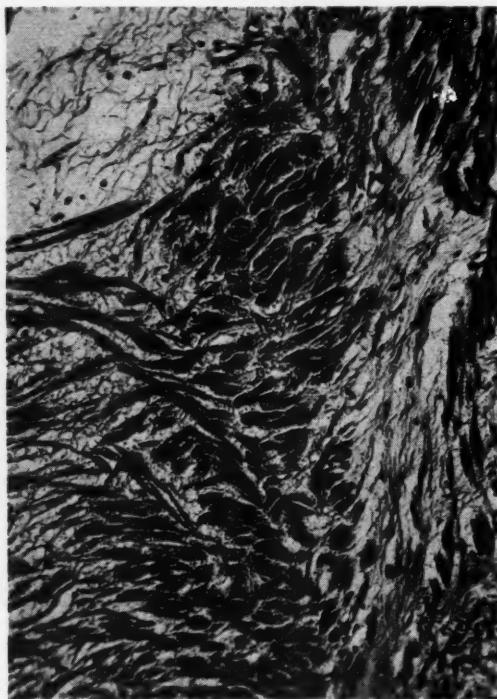


Fig. 11.—Same area as Fig. 10, showing to better advantage large media muscle cells and their penetration into the adjacent tissues.

Fig. 12.

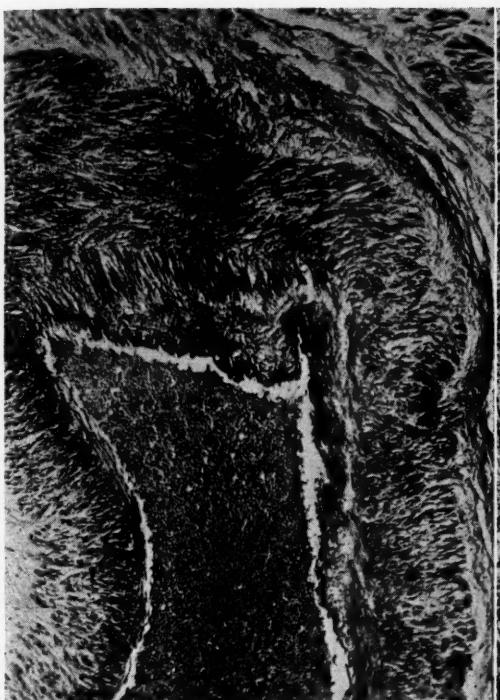


Fig. 13.

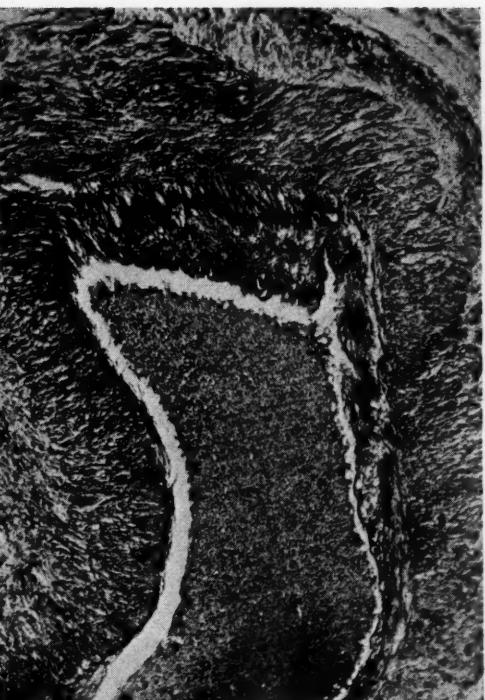


Fig. 14.



Fig. 15.



Fig. 12.—Artery, primiparous, twelve weeks' pregnancy. Marked hypertrophy and hyperplasia. Note chief change in middle of media, note parallel arrangement of cells with definite invasion in adjacent tissue at top.

Fig. 13.—Same as Fig. 12, orcein-van Gieson stain. As a result of the marked hyperplasia the internal elastic membrane is disturbed, breaking up above and appearing less significant, indicating no increase in elastic tissue.

Fig. 14.—Large hyperplastic artery, old subinvolution. Note thickness of the intima, and swollen tissue in area of the internal elastic membrane. This illustrates how even these damaged vessels can take part in this physiological process.

Fig. 15.—Same artery as Fig. 14, orcein-van Gieson stain. Note reduplication of internal elastic membrane indicating subinvolution.

Fig. 16.

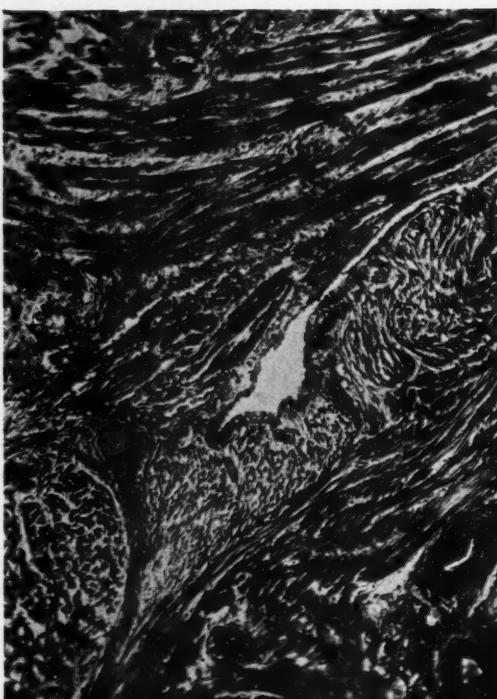


Fig. 17.



Fig. 18.

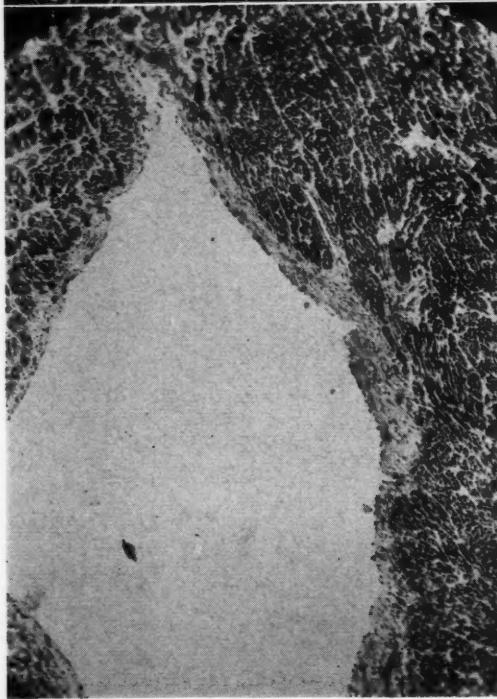


Fig. 19.

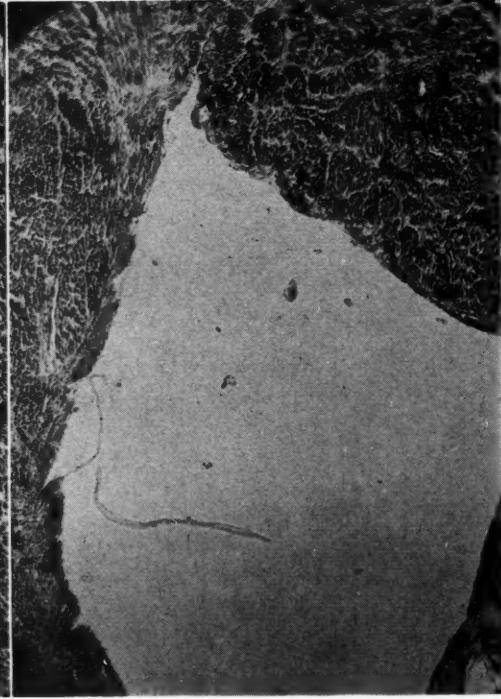


Fig. 16.—Pregnancy, six months, vein, marked hyperplasia. Note infiltration of cells is less, and the nuclei are dark and crowded. From this point further proliferation is minor.

Fig. 17.—Six months pregnant uterus. A large hyperplastic artery. Hyperplastic muscle cells are now more crowded, stain deeper, are shrunken, stage of proliferation is over, but lumen remains large.

Fig. 18.—Pregnancy, near term, uterus, vein, large sinuslike structure. The hyperplastic media have disappeared leaving a large dilated, thin-walled sac.

Fig. 19.—Same field as Fig. 18, orcein-van Gieson stain. Practically no elastic tissue is seen, indicating it takes no part in the hyperplastic process.

In this way the striking changes during pregnancy are more forcibly brought out, and so we compare them, first, to the nulliparous uterine arteries and veins, second, to the multiparous arteries and veins, and third, to the multiparous arteries and veins that are in a state of subinvolution, showing that these damaged subinvolved arteries and veins show these hyperplastic changes in subsequent pregnancies just as markedly as do the nulliparous vessels.

We therefore conclude that during pregnancy there are a marked hypertrophy and hyperplasia of the media of the uterine vessels, both veins and arteries. This hyperplasia reaches its height at about the sixth month and then the walls adjust themselves through a change which may be described as a process of stabilization toward term and preparation of the vessels for subsequent involution. Further, as these hyperplastic muscle cells are produced, they are dispersed from the vessel wall into the adjacent muscle tissue of the uterine wall, strengthening it. Likewise this invasive process runs hand in hand with the hyperplastic process in the vessel wall and becomes quiescent at the same time the vessels do. In other words, no further hyperplasia appears necessary after the second trimester of pregnancy. Sufficient cells have been laid down. Therefore, we conclude that these hyperplastic muscle cells in the uterine wall which occur quite conspicuously during early pregnancy have their origin from the media of both veins and arteries, to a greater degree in the veins.

References

1. Williams, J. Whitridge: *Obstetrics*, New York and London, 1903, D. Appleton & Co., p. 145.
2. Stander, H. J.: *Williams Obstetrics*, New York and London, 1947, D. Appleton-Century Company, Inc., p. 152.
3. Stieve, H.: *Ztschr. f. mikr.-anat. Forseh.* 17: 371, 1929.

Discussion

DR. JOHN I. BREWER, Chicago, Ill.—Certain physiologic responses are to be expected in various tissues of the body during pregnancy. Some of the most profound would logically be found in the uterus. As described by Schwarz and Hawker and others there are both hyperplasia and hypertrophy of the muscle cells of the wall of the uterus and of the muscle cells of the arteries and veins. One can certainly accept these changes as physiologic responses to the need for a larger uterus capable of more powerful muscular action and for a larger vascular system capable of accommodating a greater local blood volume. The more or less simultaneous growth of these two structures during the first six months of pregnancy as shown by Drs. Schwarz and Hawker is consistent with orderly development. The preponderance of the enlargement of the myometrium is the result of cell hypertrophy. Some, however, is due to an increase in number of individual muscle cells.

The source of origin of these new muscle cells has not been proved. Schwarz and Hawker suggest that they arise from the media of the vessels. To prove this beyond question of doubt, certain things might be helpful. Increased numbers of mitoses in the muscle cells of the media might be shown. The complete obliteration of the adventitia of the larger vessels by the muscle cells of the media as they stream toward and into the myometrium might be demonstrated by study of serial sections and comparison with vessels of various sizes. Masses of these new myometrial muscle cells and a lack of their arrangement in typical bundles immediately adjacent to the vessels would be suggestive of a center of growth. Serial section studies of the vessel walls would permit distinction between the actual outward dispersion of muscle cells and a tangentially cut section of a tortuous artery or vein wall. Similarly, a distinction could be made between the muscle cells of the media that are spreading toward the myometrium and the longitudinal smooth-muscle bundles that are often normally present in the adventitia of veins. The fact that such

muscle bundles are located in the adventitia of veins and not in the adventitia of arteries might account for the observation of the authors that there is a seemingly greater degree of dispersion of muscle cells from the media of the former.

Some veins from their inception are devoid of muscle coats. Examples are veins of bones, of the spinal pia mater, and of the maternal part of the placenta. At the placental site they are often saclike. During the early stages of implantation rather large venous sinuses without muscular tissue are abundant in the endometrium. Without doubt these structures which never had muscular walls are destined to be the large saclike venous sinuses of the mature maternal placenta.

The dependence of the growth of the vascular structures in the myometrium upon the secretion of progesterone by the corpus luteum of pregnancy as stated by the authors is in keeping with the known tissue responses in the nonpregnant uterus. In the latter, the vascular system of the endometrium is developed to a much more advanced anatomic and physiologic state under the influence of progesterone than it is by the action of estrogen alone. During pregnancy the development is still greater. Similar changes in the vessels within the myometrium are to be expected. Schwarz and Hawker have described them.

DR. EMIL NOVAK, Baltimore, Md.—Everybody appreciates, as does Dr. Schwarz, that the uterine muscle cells undergo hypertrophy and in the present study he has shown that there is marked hyperplasia of the muscle elements around the blood vessels. But the point of his paper—the new concept—is that from this muscle increase around the blood vessels new muscle elements are fed out to the muscularis of the uterus. This, I think, must still be considered a moot point. The hyperplasia of the blood-vessel musculature has been well shown but it has been accentuated in many of his slides because these sections are obviously cut tangentially, so that the apparent increase in the muscle elements is greater than the actual increase. The impression one gets from the slides is that the increase in muscle around the blood vessels is a localized phenomenon. I do not see much evidence of feeding out of muscle from the blood vessels to the uterine muscularis. You may remember that in a paper previously presented before this Society Dr. Schwarz suggested that myomas may arise from this same vascular musculature. With this new work we would have to assume that the probably transitory muscle changes around the blood vessels are responsible not only for the production of real tumors but also for the physiologic increase of the uterine musculature during pregnancy. These, I believe, are still debatable questions as I am sure Dr. Schwarz realizes. I hope—and we all hope—that he will be spared to pursue these interesting investigations.

DR. EDWARD A. SCHUMANN, Philadelphia, Pa.—In viewing these slides and others made with the same histological process, I believe that such hyperplastic muscle cells cannot, from the very nature of the mechanism, constitute an important addition to the musculature of the uterus itself. I feel rather, that this thickening of the muscular elements about the vessels is indeed a protective mechanism developed by nature to add additional protection to the vessel walls so as to prevent their compression during the tremendous contractions of the uterus during labor.

DR. T. K. BROWN, St. Louis, Mo. (Closing).—I feel as some of you do that Dr. Schwarz may not have proved his point 100 per cent but he is certain that his idea will work and is so enthusiastic about it that we may in time see him prove it.

I have studied the original slides from which these lantern slides were made and they show the point Dr. Schwarz is stressing very well. In those sections you can see the cells are almost ready to take off into the uterine wall. Perhaps he can prove it sometime.

I would feel that Dr. Schumann's idea about the increased thickness of the arterial wall is a point well taken. The arteries do not break down in the same degree or manner as the veins and Dr. Schwarz feels that from the hyperplastic veins there is a breakdown of cells which wander out into adjacent musculature of the uterus, giving it greater bulk during pregnancy.

BACTERIOLOGICAL STUDIES IN SALPINGITIS WITH SPECIAL REFERENCE TO GONOCOCCAL VIABILITY*

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FOR many years the problem of salpingitis has played a large role in the management of gynecological and obstetrical patients. However, due to extensive educational programs conducted by the American Tuberculosis Society, the U. S. Department of Public Health, and in a great measure to the untiring efforts of the American physician, there has come about a decline in the incidence of these tubal infections. Added to these splendid educational activities we now have on hand real weapons of destruction, namely, chemotherapy and antibiotics. These "wonder drugs" have truly revolutionized the problems presented in the various types of pelvic infections.

Physicians have noted the frequency of recurrent pelvic inflammatory disease, which may exist over a long period of time, when the etiological factor has been the gonococcus. With this organism as the infecting agent, it has been observed that many acute pelvic processes would, in a comparatively short time, become quiescent and asymptomatic; whereas the urethral, cervical, and Bartholin's gland infections would exist for months or even years. The main point of interest which stimulated us to carry out this investigation was whether the repeated attacks of salpingitis were due to reinfections, from a distant source, or whether they were recrudescences of a residual infection. From our observations there has been a paucity of investigation on this subject and above all no unanimity of opinion.

Menge, in 1897, was one of the first to report his findings on the incidence of organisms occurring in purulent salpingitis. He found 21.7 per cent of specimens were positive. About the same time Hyde reported an incidence of positive cultures in 18.9 per cent of cases, while Andrews reported 22.0 per cent positive cultures in his series. These quotations are from Crossen, references not given. As will be noted, these reported figures were quite uniform as to incidence. It was not until the work of Curtis,¹ in 1921, that disagreement was presented as to the high incidence of tubal organisms. Curtis, carrying out an exhaustive study, found the gonococcus was present in 19 out of 192 specimens investigated, or 9.89 per cent. He also came to the conclusion that the Neisserian diplococcus in the Fallopian tube was comparatively short-lived, the culture becoming sterile 10 to 14 days after the acute symptoms had abated and that, therefore, the tube was not a focal point of infection, the flare-ups being true reinfection from the lower genital tract. Curtis states that proof of persisting gonococcal infection deep in the tubal wall is lacking. For this reason the Fallopian tubes were thoroughly ground and then cultured. The finding of only 19 positive cultures, obtained by this method, substantiates his views as to the short life span of the organism in the tube. His list of tubal positive

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cultures was 38, of these the gonococcus was found in 19; nonhemolytic streptococcus 5; hemolytic streptococcus 4; anaerobic streptococcus 5; *Bacillus coli* 3; mixed growth 3; *Bacillus proteus* 1; tuberculosis 9.

To our knowledge no further investigation was carried out on this subject until 1938 when Studdiford and co-workers² published their findings on the longevity of the gonococcus in the Fallopian tube. His method of procedure is, briefly, as follows: Inflamed tubes and ovaries were removed at operation from 24 consecutive patients who had been afebrile for at least two weeks. Cultures were obtained from the lumina of the tubes with a platinum loop, small pieces of exudate and tissue were taken, and cultures made from pus, if present. Media used was 5 per cent horse blood-agar, hydrogen concentration 7.5. Plates were examined in 24 to 48 hours. Gonococcus complement-fixation tests were performed in 20 of the 24 cases and were found not a reliable index of infection. Results: Among the 24 cases studied there were 16 positive cultures of gonococcal infection, or, in 66.6 per cent, "Positive cultures were obtained only from pieces of tissue and exudate. Cultures from pus were negative for gonococci."

Having presented two reports of divergent results we wish to present our observations and findings on gonococcal salpingitis. Before presenting our bacteriological data we wish to discuss the problem of gonococcal salpingitis as it exists in our Department of Gynecology, at the University of Maryland.

Material

The following statistics cover a period of 10 years, from 1939 to 1949. During this period, 15,818 new patients were screened through our Out-patient Department. Of these we found 5,619 patients with evidence of gonococcal disease, which made a percentage incidence of 35.5. The infection existed in the following categories:

Salpingitis, chronic	2,980
Salpingitis, acute	499
Salpingitis, subacute	656
Pyosalpinx	50
Hydrosalpinx	21
Tuboovarian abscess	351
Pelvic inflammatory disease	1,062
Total	<u>5,619</u>

Of this group, 1,069 were admitted to the hospital for operation of various types, always with the thought that conservation should be the watchword. From these figures it will be noted that the operative index is 18.0 per cent. We feel that the indications for operative interference in gonococcal disease are as follows: (1) menometrorrhagia associated with marked dysmenorrhea; (2) painful, fixed, retrodisplacements; (3) adhesions with symptoms; (4) large hydrosalpinx or tuboovarian abscesses; (5) repeated attacks of infection.

When salpingitic lesions are of short duration and there is little associated fibrosis, splendid results are obtained by the use of chemotherapy and antibiotics, the patient frequently becoming asymptomatic. However, sterility usually ensues. If the patient has had only one mild tubal infection it is possible that pregnancy may take place if there is eventual complete regression and patency of the tube comes about. The work of the late Franklin P. Mall,³ on tubal disease in relation to ectopic pregnancies, tends to support this belief. He reasons as follows: "Tubal pregnancy usually takes place in women who have given birth to a child and then have been sterile for a considerable period. The occurrence of tubal pregnancy indicates that the inflammatory process in

the tube is gradually disappearing so that if tubal pregnancy had not taken place the chances are that the tube would eventually have become healed, thus permitting the fertilized ovum to reach the uterus."

We now wish to present the results on our studies of the bacteriology of salpingitis with special regard to gonococcal longevity. The selection of patients was of the greatest importance; obviously we would not operate on frank acute conditions unless there were some definite indication. The therapeutic use of chemotherapy and antibiotics was contraindicated for by such procedures we would definitely change the bacteriological findings.

The personnel of our Out-patient Department and Hospital Service is predominantly made up of the Negro race. As the incidence of uterine fibromas associated with gonococcal disease is here very high we selected many of our patients for study from this group. In our study comprising 80 patients, 74 were of the Negro race and 6 were white. Uterine myomas were an associated lesion in 51 instances.

EXTRATUBAL PATHOLOGY

1. Fibroids	51	63.75%
2. Ovarian cysts	12	15.0 %
3. Chronic cervicitis	4	5.0 %
4. Retroversion	3	3.75%

Method of Procedure

Smears and cultures were obtained with the platinum loop from the urethra, the cervix, and the tubal lumen in all cases. Sections of the tubal wall were also macerated and cultures then made. These procedures were carried out in a glass box, the interior of which was exposed to ultraviolet light in order to obviate atmospheric contamination, the efficiency of which was demonstrated by obtaining sterile cultures after a 30-minute exposure to the ultraviolet ray. The cultures of the tubal lumen were made on chocolate agar; the cultures of the macerated tube were made on trypticase soy broth and chocolate agar. All cultures were incubated under 10 per cent carbon dioxide tension and were reported after four days' incubation. The maceration was carried out in a sterile mortar using sterilized sand and water.

A tabulation of the bacteriological findings in 80 patients now follows:

1. Positive gonococcal cultures and source of origin:	
Urethra alone	4 5.0 %
Cervix alone	9 11.25%
Urethra and cervix	20 25.0 %
Total	33 41.25%
2. Fallopian tubes:	
Alone	0 0
One tube, cervix, and urethra	2 2.5 %
Both tubes, cervix, and urethra	2 2.5 %
One tube and cervix	1 1.25%
Total	5 6.25%
3. Fallopian tubes, sterile	61 76.1 %
4. Cervix sterile	2 2.5 %
5. Urethra sterile	3 3.75%
6. Number of tubes with positive cultures of <i>E. coli</i>	4
Number of tubes with positive cultures of staphylococci	9
Number of tubes with positive cultures of streptococcus gamma	2
Number of tubes with positive cultures of gram-plus rod	2
Number of tubes with positive cultures of yeast contaminants	1

The pathological investigation of the tubes removed presents a number of interesting facts. Tuboovarian abscesses were found in 9 instances and the bacteriological studies of the tube showed no evidence of the gonococcus. This is in contrast to the findings in the lower tract for in this group 6 of the patients had positive gonococcal cultures in the urethra and cervix and 2 of these had received courses of sulfonamide therapy and penicillin but in spite of this the cultures remained positive. All tuboovarian specimens studied showed evidence of repeated attacks as demonstrated by the marked fibrosis of the tubal wall. Varying degrees of chronicity were found in 66 tubes; here was found evidence of scarring, fibrosis, lymphoid infiltration and obliteration of the lumen, with closure of the fimbriated end and isthmica nodosa; 7 patients showed hydrosalpinges. No pus was found in the tubal lumen in any case. There were 7 patients in the semiacute status, these having definite reinfections as symptoms had extended over a number of years in each patient. In this group 5 patients had positive gonococcal cultures in the cervix and urethra. None of the 7 had positive tubal cultures for gonorrhea.

From this study we find that persistent gonorrhea in women is a disease primarily of the lower generative tract as evidenced by the fact that of the 80 patients carefully studied 33, or 41.25 per cent, showed positive cultures in the cervix and the urethra. We have also observed that cultures obtained as stated above are more reliable, as an index of infection, than the smear technique.

Why is the diplococcus so shortlived in the Fallopian tube and so long lived in the urethra and cervix? At first glance one might postulate that changes in pH play a role in the maintenance and destruction of the gonococcus in the Fallopian tube. This is borne out in vulvovaginitis in children for the gonococcus grows luxuriantly when the vaginal secretion is alkaline, i.e., pH of 7.0 plus, and the vaginal epithelium is immature; whereas, after puberty, the secretion becomes acid in the order of 4.5, due partly to the Döderlein bacillus, and the vaginal epithelium becomes mature and resistant to infection. It is thought that such conditions are inimical to the growth of the gonococcus and the infection soon disappears.

This sounds very plausible with the exception of the fact that a continued low tubal pH would sound the death knell for the spermatozoa and sterility would be more likely the rule. Wishing to learn if variation in pH in the urethra, cervix, and Fallopian tubes had any bearing on the longevity of the gonococcus we have recently instituted a series of pH studies. The determination of the pH in situ is quite simple and is obtained in a few minutes with the use of the Beckman pH meter, the sterile electrode being inserted into the urethra, the cervix, and Fallopian tube. To date we have not examined a sufficient number of patients to make a definite statement but, in general, the readings have shown slight acidity, many being nearly neutral and a few showing alkalinity. Readings obtained from the urethra, cervix, and tube are as follows: vaginal readings varied from 4.33 to 6.90 units; cervical readings varied from 6.51 to 7.27 units; urethral readings varied from 5.27 to 7.34 units.

From this preliminary observation it would appear that variation in pH in the adult plays an unimportant role in the presence or absence of the gonococcus. We will continue our investigations on these structures during normal cyclical phases and under various pathological conditions.

In summarizing our work on gonococcal infections we feel that every effort should be concentrated upon eradicating the infection in the urethra, cervix, and Bartholin's glands to prevent ascending disease. One immediately observes the great disparity between the incidence of infection in the lower generative tract and that existing in the tube. The infection in the cervix and urethra may exist for years without tubal involvement.

We know from the work of Lamar and associates⁴ that human cervical mucus undergoes cyclic penetrability to the spermatozoa and that this phenomenon occurs most markedly at the time of ovulation. They also showed that the menstrual discharge was penetrable by spermatozoa but the mucus of the phase between menstrual and midcycle is relatively impenetrable and that of the phase between midcycle and the subsequent period is impenetrable. The period of penetrability was between the ninth and the nineteenth days, but this period may be restricted to four days. From this study we may deduce that there are two optimum times for bacterial ascent, namely, at the time of ovulation and also at the menstrual time.

From our observations salpingitis is more prone to develop during menstruation for the minimal uterine contraction present at this time tends to eject uterine fluid with contained organisms into the Fallopian tubes. Acute endometritis, due to the gonococcus, is rarely seen due to its monthly shedding and rebirth.

In order to make our presentation on salpingitis more comprehensive we wish to highlight some of the important findings in tubercular and streptococci infections that have come to our attention.

Tuberculous Salpingitis

A few remarks on this subject are of interest to us primarily because of its apparent infrequency. In a survey of 1,069 patients with salpingitis, from 1939 to 1949, there were only 19 cases due to the tubercle bacillus, an incidence of 1.7 per cent. The majority of authors state the occurrence of tuberculous salpingitis to be in the order of 5 to 6 per cent; this decline we feel is, in a large measure, due to education of the public as to preventive measures, i.e., routine x-rays of the chest, improved housing facilities, etc. Some years ago the second most common cause of death was tuberculosis, whereas today this disease occupies the fifth position. There is a definite decrease in the incidence of pulmonary tuberculosis, the prime etiological factor in the development of tuberculous salpingitis, as shown by figures obtained from the Department of Health of the State of Maryland. The decrease is striking in the white race but not so significant in the Negro. In the years 1921 to 1925 the death rate per 100,000 was 94.3 for whites and 281.4 for Negroes. Many factors play a role in the high Negro rate such as substandard housing, crowding and under-nourishment, etc. Now compare these figures to those prevailing from 1941 to 1945; here we find the decline in the white race from 94.3 to 39.6 per 100,000 population, whereas the decline in the Negro race is from 281.4 to 184.7 for the same period.

An analysis of our 19 patients with tuberculous salpingitis shows an incidence of 1.7 per cent, which follows the usual pattern. It appears to occur comparatively early in life, 12 patients being in the second decade, 5 in the third, and 2 patients had the disease at 16 and 14 years of age respectively. The average duration of sterility was 7.7 years. The menstrual histories showed oligomenorrhea, menometrorrhagia, and dysmenorrhea; none had amenorrhea. As is the usual fact most of the diagnoses were made at operation and by microscopic diagnosis. We were fortunate in making a preoperative positive diagnosis in 6 patients. X-ray examinations for pulmonary disease were carried out in all patients and only 2 were found to be positive.

The frequency of involvement of the pelvic organs followed the rule, i.e., tubes 18, ovaries 4, uterus 1, endometrium 3, and cervix 1. In our bacteriological study of 80 patients, all having smears and cultures of macerated tubes, no incidence of tuberculosis of the tube was detected. All of the patients were treated by operative procedure and there were no deaths.

Postoperative complications showed 3 draining abdominal sinuses which healed spontaneously. Wound infection occurred in 3, and 1 patient had a very serious reaction resulting from a transfusion error.

Infections Following Pregnancy

This includes the puerperal as well as the postabortal infections. The background information for these few remarks on puerperal infection was furnished by Dr. Louis H. Douglass, Professor of Obstetrics, University of Maryland.

During the past 10 years, 1939 to 1949, 26,928 deliveries were performed on the obstetrical service of the University Hospital and in this large group the incidence of puerperal infection was in the order of 3.8 per cent. In this clinic, puerperal infection means any elevation of temperature to 100.4° F., or more, on any two days post partum. Sulfonamide therapy was the important factor in the treatment of this group of patients during the early years; this, however, was supplanted by the use of penicillin when it became available. No patient required operation.

On reviewing the gynecological Out-patient Department cases for the period 1939 to 1949, there were found 38 patients with postabortal infection. This group was treated with sulfonamide therapy; only 2 required operation.

Summary

A bacteriological survey, with special reference to the presence of the gonococcus, has been made on 80 patients. We wished to determine whether "flare-ups" of acute salpingitis were due to reinfections arising from dormant cells in the tubal wall or from infections existing in the urethra and cervix. No chemotherapy or antibiotics were used preoperatively in this series of cases. Of the patients operated upon, uterine myomas were present in 51 instances and there were varying degrees of salpingitis noted in 73.

The bacteriological findings were as follows: positive gonococcal infections of the urethra and cervix, 41.25 per cent; Fallopian tubes showed 6.25 per cent positive. Every tubal infection was associated with infection of the cervix and urethra. The Fallopian tubes were sterile in 76.1 per cent; the cervix sterile in 2.5 per cent; and the urethra sterile in 3.75 per cent.

Persistent viable gonococcal infection is a disease of the lower generative tract; the Fallopian tube is not a focal point for reinfection, reinfection coming from the cervix and Bartholin's glands, most likely at the time of menstruation for at this period, and also at time of ovulation, the cervical mucus is penetrable.

Our preliminary observations on pH determinations of the urethra, cervix, and tubes as yet have shown nothing conclusive in relationship to the longevity of the gonococcus. In general the readings have shown slight acidity, many nearly neutral, and a few showing alkalinity.

In regard to tuberculous salpingitis, no evidence of tuberculosis was found in this bacteriological study. In a survey of 1,069 patients with tubal disease, the incidence of tuberculosis was only 1.7 per cent. This infrequent occurrence we feel is due to the great decline in pulmonary tuberculosis.

Puerperal infections are also infrequent, being in the order of 3.8 per cent.

In conclusion, we believe that gonococcal infection of the tubes is short-lived and repeated attacks of salpingitis are due to reinfection from the lower generative tract. We also feel it would not seem too speculative to believe that there will be a decreasing incidence of these infections, brought about by lay education, ever improving obstetrical practice, and above all by the use of chemotherapy and antibiotics.

We wish to express our appreciation for the wholehearted cooperation of the Department of Clinical Bacteriology, under the direction of Dr. Milton Sachs, Hospital of the University of Maryland.

We are especially indebted to Miss Audrey Funk, Chief Technician in the Department of Bacteriology, for her splendid services which have, in a great measure, made this paper possible.

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Discussion

DR. FREDERICK H. FALLS, Chicago, Ill.—It is obvious from Dr. Hundley's report that the early enthusiastic predictions that, with the discovery of penicillin and other antibiotics, gonorrhea was to become a thing of the past, have not come to pass. That we were to suffer the same rude awakening as to their shortcomings as we did with the sulfonamides and the wonder drug 606 in the treatment of syphilis early in the century might be expected. Five thousand six hundred nineteen gonorrhreal cases out of 15,818 admitted to the Maryland Clinic tells the story.

Evidently the gonococcus is still prevalent. True, the clinical course of the disease has been modified until those of us who knew the disease B.S. and B.P. (before sulfonamides and before penicillin) hardly recognize its clinical course now as it is influenced by these drugs. Still these cases are seen in our clinics and the problems as to their treatment both immediate and remote have to be met.

As pointed out by Dr. Hundley, the gonococcus tends to disappear from the Fallopian tube pus a few weeks after the acute stage of the disease. This is thought by some to be due to the modern methods of treatment. They forget that the very same thing happened when Curtis did his work before 1921, and it was well known clinically long before that. It was common practice at the County Hospital in Chicago, to close these incisions without drainage after spilling the pus from a pyosalpinx, and this was done at a time when most surgeons drained the abdomen for other pyogenic infections.

Of even more importance is the fact which has, I believe, been generally overlooked, that in these cases which we describe as gonorrhreal salpingitis we are dealing with a localized pelvic peritonitis described by most writers of textbooks, but in addition we have a general peritonitis which extends up to the diaphragm causing the "fiddle string" adhesions between the liver and the diaphragm to which Curtis called our attention a number of years ago. The real significance of this finding has not been appreciated. It is that the gonococcus biologically is a very delicate organism. One has only to attempt to grow it and to keep the culture alive to appreciate this. In order to survive it must have conditions ideal for its growth and reproduction. This implies the proper nutrition, oxygen tension, moisture, heat, and light. These favorable circumstances are met only within certain tissues, cervix, Bartholin's glands and Skene's ducts. They are not provided in the peritoneal cavity or tube for very long after the reaction to the infection has taken

place. If one adds to these facts the effect of immune bodies stimulated by the primary invasion of the organisms the reason for spontaneous recovery and the sterility of the tubal cultures becomes apparent.

As regards tuberculous salpingitis, it has always seemed to me that the figure of 7 per cent as given by Curtis was too high. We agree with Dr. Hundley and have had an incidence of only 2 per cent at Research and Educational Hospitals and no higher at Cook County Hospital. To be carefully differentiated because of its great importance to the patient, although of much rarer incidence, is carcinoma of the Fallopian tube. These are much more frequently found in older women and may be considerably larger than the average pus tube. They are often unilateral and may be associated with postmenopausal uterine bleeding. On two occasions we have made the differential diagnosis on positive Papanicolaou smears. Another lesion that is rare and usually misdiagnosed as gonorrhreal salpingitis is actinomycosis of the tube and ovary. The gross appearance is very similar. It differs in the fact that it is practically always found to be unilateral, located on the right side, and the ovary is more involved in the inflammatory process than the tube. The importance of differentiating these lesions is that unless the uterus and other tube and ovary are removed they will become involved and a fatal result is almost inevitable.

We have recently treated a series of cases of tuberculous salpingitis and peritonitis at Cook County Hospital with streptomycin. In general the results were very good as compared with other methods of management previously employed. We were struck by the general improvement of the patient and also by the lytic effect on the dense local adhesions in the pelvis and lower abdomen. This rendered access to the tubes and their surgical removal very much easier and less dangerous.

DR. WALTER DANNREUTHER, New York, N. Y.—I can certainly agree with Dr. Hundley regarding the present lower incidence of gonococcal salpingitis as contrasted with that of some twenty-five years ago. The survival of gonococci in the endocervix, Bartholin's and Skene's glands, is explained by the fact that these are compound racemose glands in the deep recesses of which the organisms tend to conceal themselves whereas the endometrium is composed of simple tubular glands. It has been difficult to demonstrate that infection reaches the tubes by continuity of surface and that there is ever any true gonococcal infection of the endometrium. It seems logical to assume that many of these recrudescences are due to lymphogenous spread from the endocervix.

In regard to tuberculous salpingitis, I believe that, if salpingectomy is to be done, the uterus should be included in the operation. I have seen several instances in which salpingectomy has been performed elsewhere, and within one to five years the patient has presented herself with bleeding. Endometrial and cervical biopsies are usually negative, but hysterectomy shows extensive tuberculous involvement of the endometrium.

DR. HUNDLEY (Closing).—We are heartily in accord with Dr. Falls' statement as to the importance of medical therapy prior to operation. All patients showing gonococcal disease received bed rest and chemotherapy. As we all know, time plays a great role in the elimination of gonococcal salpingitis. As above stated, our operative incidence for gonococcal disease is 18.0 per cent. It is possible that in the future, with more concentrated use of penicillin, this operative index may be considerably lowered. We, in our clinic, are great believers in the conservative approach to all gonococcal problems.

In regard to Dr. Dannreuther's remarks regarding gonococcal infection of the tube occurring by way of the lymphatic system, I have always been of the opinion that the gonococcus migrated upward over the endometrium and thus involved the tubal mucosa. The cyclical shedding of the endometrium and its rebirth from the basal glands accounts for the infrequent occurrence histologically. If the migration of the organism is by the lymphatic channels the infection would be prone to be perisalpingitic and not mucosal. As we all know, repeated attacks of salpingitis occasion fibrosis of the tubal wall but the initial attack is primarily confined to the mucosa.

THE SQUAMOUS EPITHELIUM AND SQUAMOCOLUMNAR JUNCTION OF THE CERVIX DURING PREGNANCY*

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ALTHOUGH frequent reference has been made to the difficulty in the histologic interpretation of cervical abnormality in pregnancy, relatively little study has been devoted to defining the ordinary changes which occur in the squamous epithelium in pregnancy, or to the setting of limits of normality. In a recent study of cervical biopsies taken during pregnancy, Carrow and Greene¹ were unable to find any constant changes which could be considered specific to pregnancy. Maino, Broders, and Mussey² confirm the findings of Hofbauer³ and Levey,⁴ namely, a hyperplasia of the squamous epithelium of the portio. They suggest that there should be no difficulty in recognizing the pregnancy reactions of the cervix as benign tissue phenomena, and find the cells to be uniform and regular and the growth orderly. Mitoses were occasionally found in the basal cells, but abnormal mitoses were absent. The staining characteristics were typical of those found in benign tissue. Sheets,⁵ from the study of cervical biopsies, found deviations from the accepted normal in 45 per cent of specimens. This incidence was considered to be higher than is found in nonpregnant cervices, and although the findings were similar to those encountered in the nonpregnant, the high rate of deviations is inferred to be due to pregnancy. Murphy and Herbut,⁶ in a study of biopsies from the squamocolumnar junction of the cervix in pregnancy, found inflammatory changes in this area in 42 per cent of cases. Epidermization, either at the external os or within the cervical glands, occurred in 18 per cent. In all cases the squamous epithelium was thickened, and in six per cent there was evidence of basal-cell hyperactivity. No comparison was made with nonpregnant tissue. Although an unstated number of these cervices were grossly healthy, these findings were statistically and qualitatively comparable to those of Fluhmann,⁷ whose material consisted of 89 biopsies from pregnant cervices which were grossly abnormal. Similarly, Fluhmann found that both epidermization and hyperactivity of the basal layers of the squamous epithelium were especially prone to occur in pregnancy, although no specific comparison with nonpregnant tissues is presented. In the instance of basal hyperactivity, there was considerable variation in the size of the cells, and mitoses were frequent. Hofbauer's findings were comparable. Edmonson and others⁸ made a detailed analysis of five papillary lesions of the cervix in pregnancy, and concluded that although similar lesions occur in the nonpregnant, the presence of pregnancy

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appears to alter such lesions by an increase in the mitotic activity and an increase in hyperchromatin and inequality in size of the nuclei. They also found the rate of mitosis in the squamous epithelium of the cervix to be greater in the pregnant than in the nonpregnant uterus.

With the exception of these articles, there is little in the literature to indicate the changes which might logically be expected to occur in these tissues as the result of pregnancy. The purpose of this study is to present the histological findings in the squamous epithelium and squamocolumnar junction of the pregnant cervix, to compare these with the findings in a series of nonpregnant cervices, and to indicate the deviations from the accepted normal.

Materials and Methods

The material consisted of 22 pregnant and 46 nonpregnant uteri. All of these were removed surgically.

Pregnant Uteri.—The gestation periods varied from one to five months. The specimens were removed for purposes of therapeutic abortion and sterilization. They were normal except for the occasional incidental presence of small fibroids. Significant cervical disease was not a prominent feature in any. Bouin's fixation was employed. In most of the specimens multiple (two to six) blocks were cut from the cervix after fixation, and sections were stained according to the following techniques: hematoxylin and eosin, mucicarmine, iron hematoxylin, Best's carmine, reticulum, and Milligan's trichrome. In so far as possible the blocks were placed so as to avoid tangential section of the squamous epithelium of the portio.

Nonpregnant Specimens.—All of these were removed for reasons other than cervical disease, as part of routine complete hysterectomy. The cases selected for this control group were those with minimal or virtually absent gross cervical findings. Special stains were employed in only six of these specimens, the remainder being studied with hematoxylin and eosin.

For purposes of study the thickness of the squamous epithelium was divided into three zones: the basal zone, which corresponds approximately to the lower one third; the mid-zone, or glycogen-containing portion, corresponding approximately to the middle one-third; and the superficial zone, comprising the upper one-third. The pregnant group was studied first, with the view to obtaining a general picture of any deviations from the accepted normal. It was not until the completion of this preliminary survey that the necessity for a control group became apparent. Although the normal picture has been described on frequent occasions, the outer limits of normal are less clear, and as they have been described are not satisfactory for a study such as this. Accordingly, the nonpregnant series was studied, and served as a control for the findings in the pregnant group.

Results

General Appearance.—There were no evidences of malignancy, either invasive or intraepithelial according to accepted criteria^{9, 10} for these diagnoses, in any of the cervices studied. In the pregnant group, particularly, the deviations from normal tended to occur within a radius of 5 to 6 mm. about the external os: the peripheral portions of the cervix generally conformed more strictly to the accepted normal. In the instance of multiple blocks and slides from the same cervix, the findings in all were, for the most part, uniform; it was unusual to find significant differences in the various radial planes of the individual cervices.

All of the photomicrographs are from the pregnant group.

Total Thickness of the Squamous Epithelium.—In most cases, both pregnant and nonpregnant, the epithelium was somewhat thicker peripherally than centrally, but there was no significant difference in thickness in the two groups. Measured at a point about midway between the external os and the vaginal reflection, the average thickness in the pregnant group was 294 microns (the extremes being 168 and 364 microns), and in the nonpregnant 252 microns (with extremes of 112 and 448 microns).

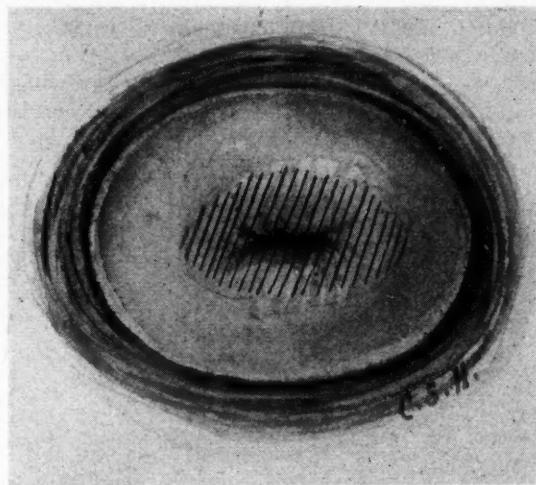


Fig. 1.—For the most part, deviations from the normal occurred within a radius of 5 to 6 mm. about the external os. This is referred to as the "central portion" of the portio, in contradistinction to the "peripheral" portion, where the epithelium showed fewer deviations.

Basal Zone.—As it is ordinarily described, the basal zone consists of (a) a single layer of cylindrical cells with elongated nuclei, and (b) four to six layers of polyhedral or cuboid cells which are superimposed upon the basal layer. The cells above the basal layer have fairly large nuclei of generally uniform size, shape, and staining reaction, and distinct cell outlines between which intercellular bridges are usually evident. The basal layer of cells is generally considered to lie upon a basement membrane. Although the existence of such a membrane is denied by some,¹¹ Maximow¹² states that it is often difficult to see in routine preparations. It consists of a connective tissue condensation of amorphous substance and reticular fibrils, and was regularly demonstrated to my satisfaction by means of trichrome or reticular stains.

a. *Shape of basal layer cells:* In 74 per cent of the nonpregnant specimens the basal nuclei throughout were approximately uniform whereas in the remainder they were more ovoid centrally, and more elongated peripherally. The findings in the pregnant group were virtually reversed, the nuclei throughout being approximately uniform in only 27 per cent, while in 73 per cent the peripheral nuclei were significantly more elongated than those covering the central portion of the cervix (Figs. 6 and 9).

b. *Thickness:* In all of the nonpregnant specimens, and in all but 8 (28 per cent) of the pregnant, the thickness of the basal zone was generally uniform centrally and peripherally, consisting of from four to eight layers of cells. In the 8 pregnant specimens, the basal zone was significantly thinner in the central portion than peripherally (Figs. 2 and 3).

c. *Disturbed polarity:* In no case was this sufficient to arouse suspicion of malignancy. It occurred in very minor and perhaps even questionable degree in 46 per cent of the nonpregnant and 59 per cent of the pregnant. There was no apparent predilection for the central portion over the peripheral.

d. Irregularity of basal zone nuclei: A judgment concerning uniformity of size, shape, and staining reaction for comparative purposes, short of a tabulation of all cells observed, is necessarily inexact. However, as judged by inspection, generally good uniformity of the basal zone nuclei was present throughout in 78 per cent of the nonpregnant cervices, and in 32 per cent of the pregnant. The larger nuclei in the nonpregnant averaged 7 by 8.4 microns, while in the pregnant the larger nuclei averaged 9.8 by 11.2 microns; the largest basal zone nucleus which was seen, 14 microns in diameter, occurred in one of the pregnant specimens. As a rule, discrepancies in size, when they occurred, were more usual in the central than the peripheral portion of the cervix in both pregnant and nonpregnant. Differences in staining reaction were not marked in any of the specimens, although minor discrepancies were somewhat more frequent in the pregnant group.

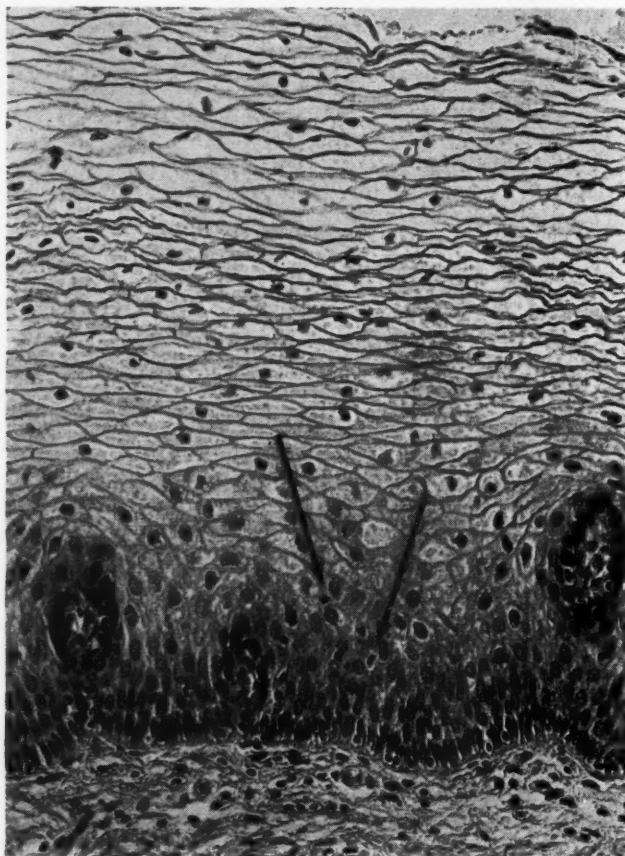


Fig. 2.—Squamous epithelium, peripheral portion of cervix. Generally normal throughout its thickness. Two mitotic figures high in basal zone. Most of the basal zone nuclei have one or two nucleoli. (H. and E. stain, $\times 840$.)

e. Nucleoli: The presence of multiple nucleoli was a much more prominent feature of the pregnant than the nonpregnant cervices. In the latter, the majority of the nuclei contained either one nucleolus or none. In those without a nucleolus the chromatin fragments were finally or moderately granular. Multiple nucleoli were present infrequently. In the pregnant group, multiple nucleoli were frequent in 41 per cent of the cases. Also, the frequency of coarsely

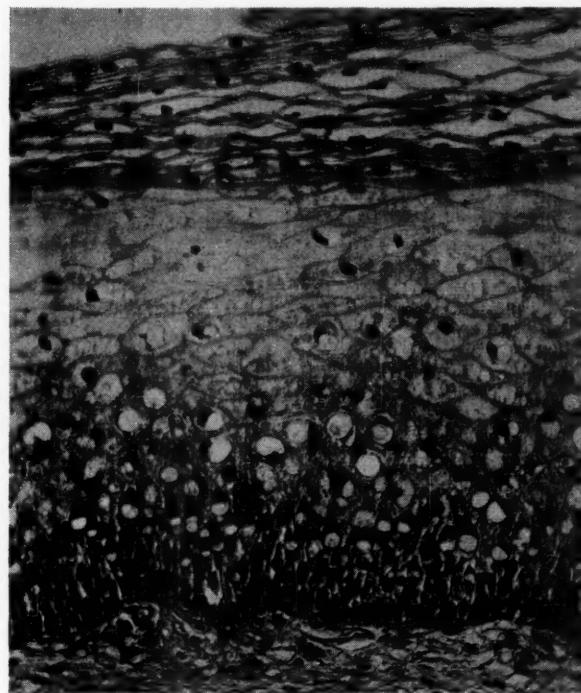


Fig. 3.—Same slide as Fig. 2, central part of cervix. Squamous epithelium thinner, many vacuolated nuclei in upper basal and lower mid-zones. ($\times 840$.)

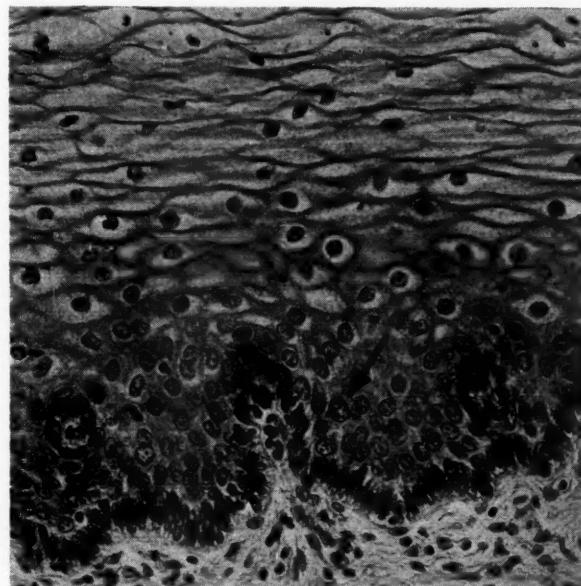


Fig. 4.—Basal layer of nuclei elongated, basal zone nuclei showing uniform staining reaction but much variation in size. Mid-zone nuclei show slight shrinkage in most cases although several active nuclei can be seen. (Iron hematoxylin stain, $\times 885$.)

granular chromatin clumps or condensations was greater in the pregnant than in the nonpregnant group (Fig. 4).

f. *Mitotic figures:* No abnormal mitotic figures were seen in any of the tissues. Mitotic figures were not observed at all, or were extremely rare, in 87 per cent of the nonpregnant specimens, and in 36 per cent of the pregnant.

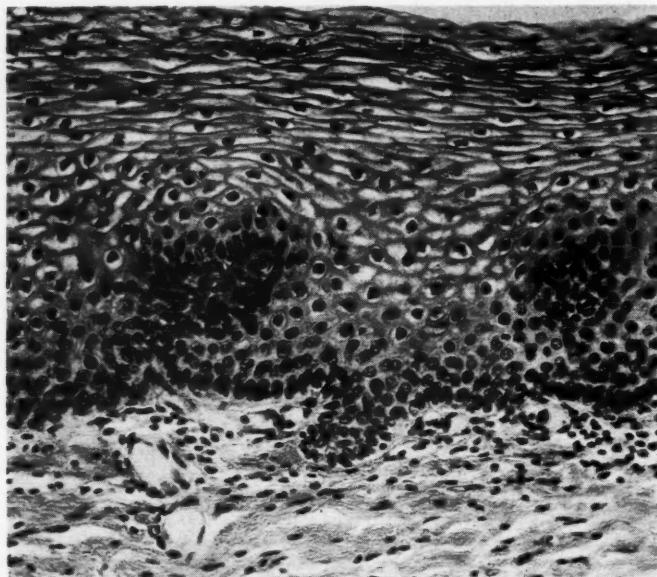


Fig. 5.—Epithelial bud near highest convexity of portio. Thickness of epithelium is reduced. Basal-layer nuclei ovoid rather than elongated. Basal and lower mid-zone nuclei show fair uniformity in staining reaction, but slight variation in size and shape, mostly one nucleolus, and several coarsely granular chromatin clumps. (H. and E. stain, $\times 750$.)



Fig. 6.—Thin epithelium near external os. Basal layer greatly flattened. Some variation in staining reaction of basal zone cells. Active-appearing nuclei in mid-zone. (H. and E. stain, $\times 750$.)

In the remainder they were found at random throughout the basal zone. In the nonpregnant specimens the figures generally occurred in the layer of cells just superficial to the basal layer, whereas in the pregnant they were often found from one to three layers superficial to this (Fig. 2).

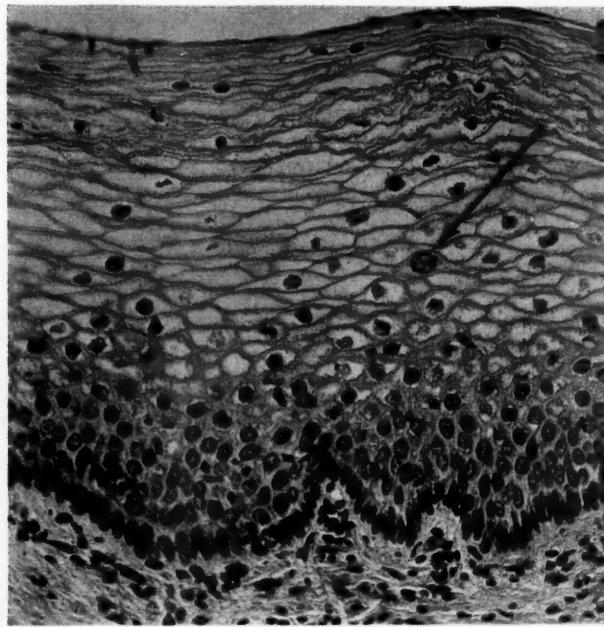


Fig. 7.—Large, healthy-appearing nuclei in mid-zone. In addition to size discrepancy, there is moderate difference in shape and staining reaction. (Iron hematoxylin stain, $\times 750$.)

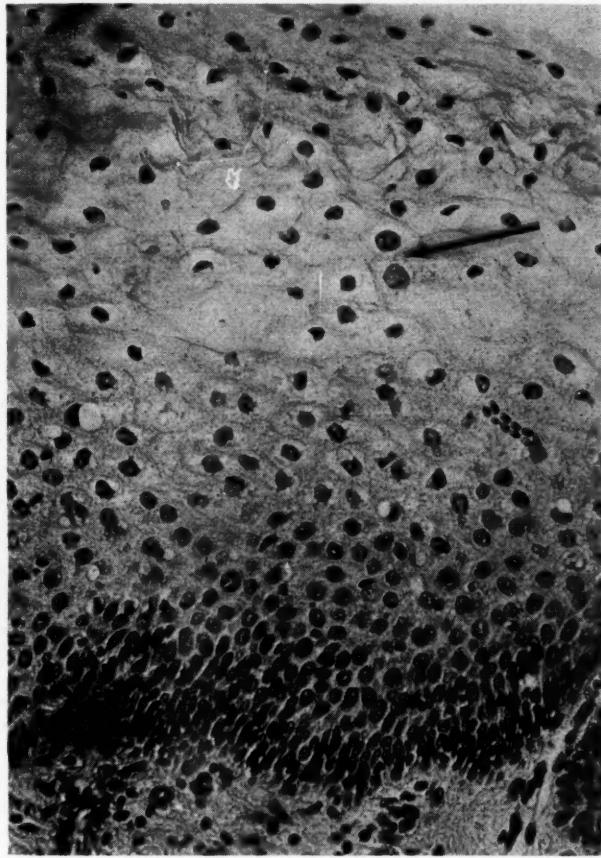


Fig. 8.—Two large, healthy-appearing nuclei high in mid-zone, with sharp outlines and coarsely granular chromatin. Some disturbance of polarity of basal zone. (H. and E. stain, $\times 870$.)

g. Epithelial buds, or downgrowths of the squamous epithelium into the underlying stroma: Excluding the downgrowths which were directed toward or associated with an underlying cervical gland, buds occurred in 30 per cent of the nonpregnant specimens, and in 64 per cent of the pregnant. There was no suspicion of malignancy in any of these.

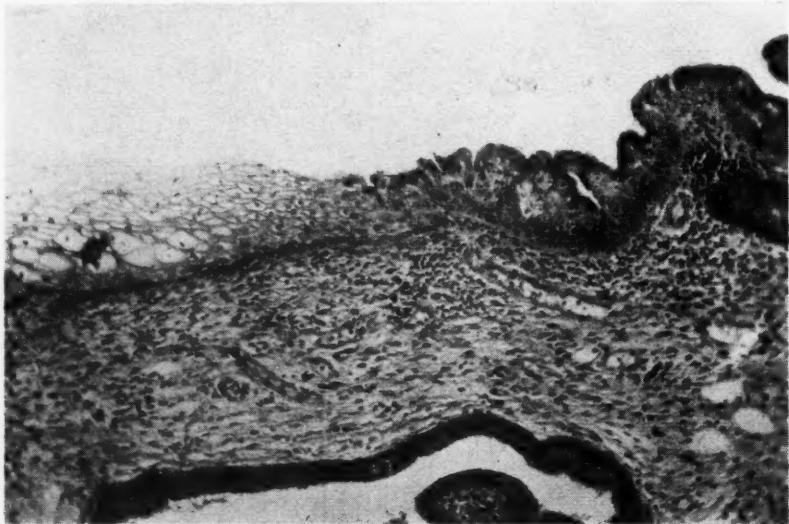


Fig. 9.—Squamocolumnar junction, showing squamous metaplasia of columnar epithelium. Note flattening of basal layer of cells of squamous epithelium. (Mucicarmine stain, $\times 350$.)



Fig. 10.—Squamocolumnar junction showing transition from squamous epithelium to squamous metaplasia. Note inflammatory reaction. (H. and E. stain, $\times 324$.)

h. Subepithelial infection: In 51 per cent of the pregnant specimens, and 53 per cent of the nonpregnant, there was virtually no evidence of infection in the subepithelial zone of the portio from the external os to the vaginal reflection. In 32 per cent of the pregnant, and 40 per cent of the nonpregnant, there were occasional isolated collections of lymphocytes and plasma cells. In the remainder,

the subepithelial zone was lightly to moderately infiltrated throughout with lymphocytes, plasma cells, and occasional polymorphonuclear leucocytes. In no case was there marked inflammation of this zone.

Fig. 11.

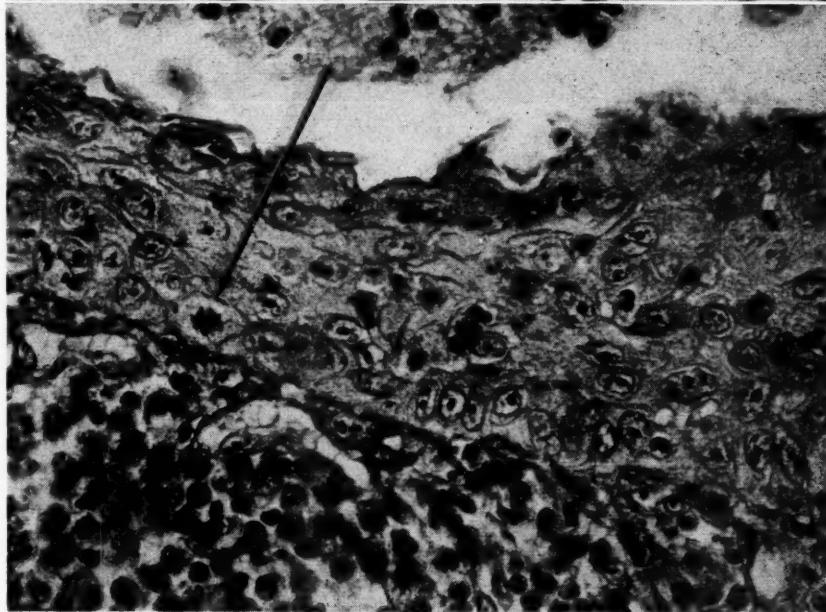
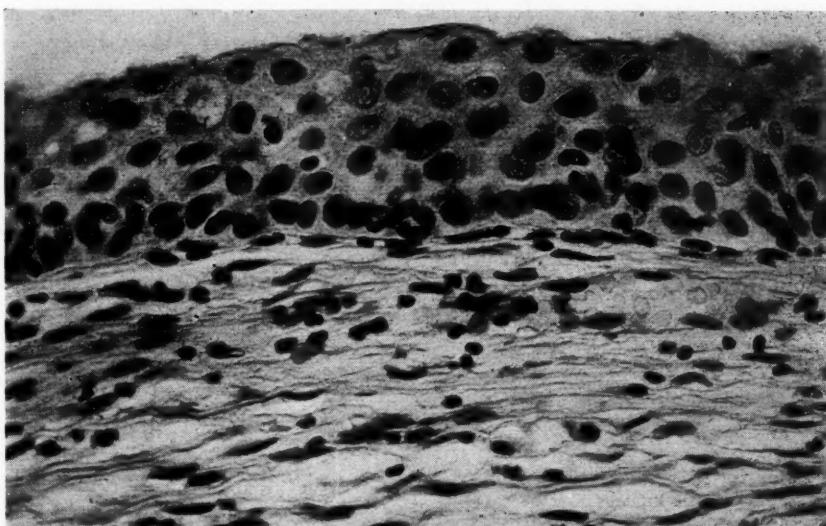


Fig. 12.

Fig. 11.—Squamous metaplasia in region of squamocolumnar junction. Considerable variation in nuclear size, but good uniformity in staining reaction. (H. and E. stain, $\times 1,602$.)

Fig. 12.—Squamous metaplasia in region of squamocolumnar junction. Variation in size of nuclei, with much clumping of chromatin granules. Large mitotic figure present. (Iron hematoxylin stain, $\times 1,605$.)

Mid-zone.—The thickness and number of layers in the mid-zone showed little significant difference in pregnant and nonpregnant. The only point of distinction was the greater frequency in the pregnant of "active" nuclei, a

term used¹³ to describe nuclei which are larger than normal, with chromatin in small dense clumps instead of finely granular. Such nuclei appeared in the mid-zone in significant numbers in 73 per cent of the pregnant cervices, and in only 13 per cent of the nonpregnant. The average size of these larger nuclei

Fig. 13.

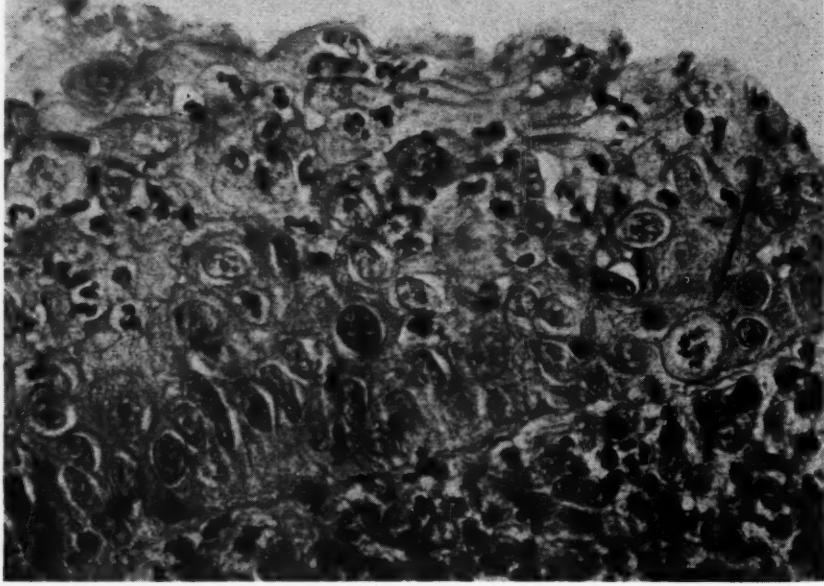
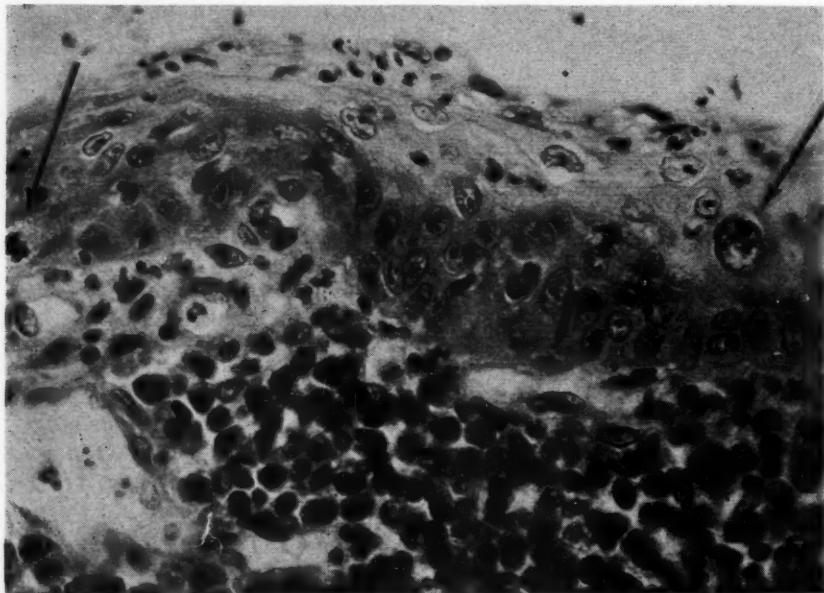


Fig. 14.

Fig. 13.—Squamous metaplasia, region of squamocolumnar junction. Mitotic figure present, fairly uniform staining reaction but much variation in size of nuclei. (H. and E. stain, $\times 1,602$.)

Fig. 14.—Squamous metaplasia at squamocolumnar junction. Large mitotic figure in basal layer of cells. Elsewhere, variation in size, shape, and staining reaction. Considerable secondary infection. (Mucicarmine stain, $\times 2,064$.)

was of the order of 5.6 by 5.6 to 8.4 microns. The largest nuclei seen in the mid-zone were 8.4 by 11.2 microns.

Superficial Zone.—In the area superficial to the glycogen-containing zone there was little difference in the two groups except for keratinization of the superficial layers, which occurred usually in slight degree in 20 per cent of the pregnant and to a more marked degree in 35 per cent of the nonpregnant.

Squamocolumnar Junction.—

Metaplasia: In 86 per cent of the pregnant cervices and in 43 per cent of the nonpregnant the transition from stratified squamous to columnar epithelium was not abrupt. Instead, in these cases a variable segment of metaplastic epithelium was interposed between. As pointed out by Carrow and Greene, this tissue for the most part is not "squamous" metaplasia, but is rather "transitional" metaplasia, in which the basal cells are generally cuboidal, and the more superficial cells are irregularly polyhedral. In the nonpregnant cervix the nuclei in these metaplastic areas tended to be more or less uniform, and mitotic figures were rare. In the pregnant, there was often rather more than slight variation in size, shape, and staining reaction, and mitotic figures were not unusual.

Subepithelial Infection.—In 95 per cent of the pregnant specimens and in 43 per cent of the nonpregnant, the subepithelial zone at the squamocolumnar junction was either moderately or markedly infiltrated with inflammatory cells. In the remainder this infiltration was considered to be insignificant (Table I).

TABLE I

	PREGNANT	NONPREGNANT
Total thickness	294 μ (168-364 μ)	252 μ (112-448 μ)
<i>Basal Zone.</i> —		
Discrepancy in basal-cell shape (more ovoid centrally)	73%	26%
Irregularity of basal zone nuclei	68%	22%
Nucleoli, multiple	41%	Rare
Mitotic figures	64%	13%
Epithelial buds	64%	30%
<i>Mid-zone.</i> —		
Active nuclei present	73%	13%
<i>Squamocolumnar Junction.</i> —		
Surface metaplasia	86%	43%
Inflammatory reaction	95%	43%

Comment

In any study concerned with small groups of data, the possibility of chance or random selection is present. This work is not an exception, and unfortunately the data do not lend themselves to statistical interpretation. Although the differences between the pregnant and control groups were striking, they represent only the findings in these particular uteri; the final decision as to whether the changes are wholly typical must await the appearance of other similar series of cases. But it is probable that these specimens are representative, for the findings are quite reasonable.

Although no changes were found in the cervix during pregnancy which were not also demonstrable in the nonpregnant, nevertheless, the incidence of certain deviations was different in the two groups. Differences in the size, shape, and staining reaction of the nuclei in the basal and metaplastic zones, mitotic activity,

the presence of active nuclei in the mid-zone, and infection and metaplasia at the squamocolumnar junction were all more frequent in the pregnant group, and apparently significantly so. Also, epithelial downgrowths into the underlying stroma, and the presence of multiple nucleoli and coarsely granular chromatin clumps were much more frequent in the pregnant group.

The deviations which occurred with greater frequency in the pregnant group are clearly in the direction of hyperactivity as defined by Galvin and Te Linde¹⁴ and by Young and others.¹⁰ Since these evidences of hyperactivity are more frequent in the pregnant group than in a comparable nonpregnant group, it is reasonable to consider them reversible. How far such changes must progress before they become irreversible has not been determined. Hertig¹⁵ has referred to the element of confusion which pregnancy may interject into cervical pathology. This confusion appears to stem primarily from the evidences of hyperactivity which have been outlined here. Since these changes are considered to be due to pregnancy, and are thought to be for the most part reversible, it is emphasized that during pregnancy one's attitude toward equivocal or borderline cervical cancer should be particularly conservative, for the possibility of regression of such suggestive lesions would appear to be at least as good as the possibility of progression to frank malignancy. Also, regression of this type of lesion as occurred in Hill's case¹⁶ would seem to be more probable in the pregnant than in the nonpregnant cervix.

Summary and Conclusions

The squamous epithelium and squamocolumnar junction of 22 pregnant and 46 nonpregnant cervices were studied. All specimens were obtained by complete hysterectomy. No changes occurred in the pregnant group which could not also be found in the nonpregnant. The following discrepancies were found in the incidence of these deviations: slight to moderate irregularity in size, shape, and staining quality of the basal zone nuclei occurred three times more frequently in the pregnant than in the nonpregnant; mitotic figures were five times as frequent in the pregnant group, and tended to occur higher in the basal zone than in the nonpregnant; epithelial buds, or downgrowths into the underlying stroma, were twice as frequent in the pregnant group; multiple nucleoli and coarsely granular chromatin clumps were rare in the nonpregnant, and frequent in the pregnant; active nuclei in significant numbers were present in the mid-zone, six times as frequently in the pregnant as in the nonpregnant; squamous metaplasia and subepithelial inflammatory reaction at the squamocolumnar junction were more than twice as frequent in the pregnant group.

The relation of these changes to *in situ* carcinoma is briefly discussed. Since the deviations noted in pregnancy are hyperactive ones which are considered to be for the most part reversible, it is suggested that during pregnancy one's attitude toward equivocal or borderline cervical cancer should be particularly conservative.

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Discussion

DR. C. FREDERIC FLUHMAN, San Francisco, Calif.—In these days when special attempts are being made to review our concepts of the histologic criteria of malignancy, Dr. Danforth's study is especially welcome and his conclusions have much significance. During pregnancy the cervix responds to an intense endocrine stimulation and this is well borne out by the findings, for example, that the squamous epithelium hypertrophies, the mitotic figures were five times more frequent than in the nonpregnant group, and that multiple nucleoli and coarsely granular chromatin clumps were frequent. It is important to note that these features were observed by comparison with the cervices of nonpregnant women and that in both series there were no gross pathologic lesions. This contrasts with the study I presented before this Society three years ago where a pathologic condition existed in every instance. From the data which the essayist has given, his conclusion that the deviations noted during pregnancy are probably reversible and that one's attitude in the clinical management of women with suspected carcinoma of the cervix during pregnancy should be conservative and expectant, seems quite justified.

It is unfortunate that Dr. Danforth was forced to limit his observations to the activity of the squamous epithelium, and we must hope that in time he will extend this investigation to include the other tissue elements of the cervix. This is important, especially as regards the close interrelationship between squamous and cylindrical epithelium, which is seen not only during pregnancy but in other lesions such as erosions and various inflammations. This close relationship, it has always seemed to me, is beautifully illustrated in the rat and mouse. After castration the epithelium of the vagina in these animals becomes of a low cuboidal type in one or two layers of cells. With stimulation by adequate dosages of estrogenic hormone, these cells multiply and the surface is composed of high cylindrical cells. On further stimulation the epithelial wall hypertrophies, the cylindrical cells are pushed up and are finally discarded until a well-formed squamous epithelium ensues. If the administration of the hormone is then discontinued, the epithelium completely atrophies and resumes its previous appearance of low cuboidal cells. Certainly we can consider these transformations as of a reversible character. However, in the human being it will be difficult to determine how much recession of the changes in the cervix during pregnancy does occur. It will require many extensive studies such as the one presented this morning.

DR. RICHARD TE LINDE, Baltimore, Md.—This study of Dr. Danforth's is, I believe, a very important and fundamental one. It can be summed up in a few words and that is that there is an increased activity in the stratified squamous epithelium of the cervix in pregnant women. Dr. Danforth showed no cases in which this hyperactivity took over the entire thickness of the epithelium, presenting a picture which could be confused with carcinoma *in situ*. However, his study is on a relatively small number of cases. Dr. Hellman of our clinic has made a similar study and frequently has shown me a slide showing hyperactive epithelium and has asked, "Is this carcinoma *in situ*?" I believe the

most important question one has to ask when presented with questionable cervix slides is: Is or is not this woman pregnant? There are changes in the pregnant cervix, such as hyperchromatism and increased mitotic figures through the full thickness of the epithelium which, in a nonpregnant cervix, would indicate carcinoma in situ. I am convinced that one cannot say that they have the same significance in the case of the pregnant cervix. Hellman has six such cases followed up to two years after pregnancy and none of them has developed clinical malignancy. Subsequent biopsies have shown complete disappearance of this hyperactivity. There is one case ten months afterward that began again in the nonpregnant state to show some basal-cell hyperactivity but this is no real evidence to indicate that this picture, which occurs during pregnancy, actually represents carcinoma. To put it in another way, if you are going to make a diagnosis of carcinoma in the pregnant cervix, I believe you really have to see unequivocal invasion before being justified in making such a diagnosis. We can well adopt a very conservative wait-and-see attitude in these questionable cases. I think that the hyperactive process is at least temporarily reversible and it may be that it is permanently reversible.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—Dr. Danforth continues to add to our knowledge of the quantitative differences found in biopsy studies of the pregnant cervix, meticulously studied.

Dr. Edward J. Murphy of the Jefferson Clinic published findings in 50 such biopsies in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in February of this year. Subsequent to the original study, approximately 25 more pregnant cervices have been biopsied by the ethmoid snare technique, secured from a relatively evenly distributed group of primi- and multigravida patients. The findings in the 75 cervices studied, following which no untoward effects were observed in any of the patients, were as follows:

1. Hemisection of the nonpregnant cervix showed normal structure.
2. Increased vascularity and edema of the stroma, and increased size and number of the individual cells were seen in all specimens, 100 per cent. The endocervical mucosa revealed proliferation of the columnar epithelium and downgrowth of glands into the stroma.
3. The squamous epithelium showed increased thickness with no loss of stratification in all cases (100 per cent) but basal-cell activity was present in only 6 per cent.
4. Inflammatory-cell infiltration was noted in 64 per cent. Concentration of the reaction at the squamocolumnar junction was seen three times more frequently in multiparous than in nulliparous cervices.
5. Epidermization or metaplasia of the endocervical tissue was found in 20 per cent.
6. Decidual change in the stroma was observed in 22 per cent.

In no instance in this series was intraepithelial cancer (carcinoma in situ) found.

Case Citation.—C. H., aged 20 years, showed marked cervical erosion with first pregnancy at four months. On Feb. 12, 1946, Papanicolaou smear showed: "Abnormal cervical cells, suspicious but not absolutely diagnostic of cervical malignancy" (Rakoff). Biopsy on the same date showed carcinoma in situ (confirmed by Emil Novak) who stated: "Negative except for a single tiny nest of what appears to be a definite epidermoid cancer of the cervix. I do not see how any other diagnosis can be made in spite of the fact that the patient is only twenty years of age."

March 6, 1946: Repeat biopsy showed cervical erosion (glandular) with very marked proliferation of the squamous epithelial zone (Hoffman).

There were argument and controversial factors with respect to treatment. Therapy for cancer was refused by the patient pending return of her husband from a voyage on a tanker and there was a long delay in decision because of this. An elective cesarean section was decided upon.

July 18, 1946: A low-flap cesarean section was performed and a viable and healthy child delivered. The patient had a normal postoperative course.

Oct. 15, 1946: Following complete involution, circular biopsy and fairly wide excision of the cervix were done to include the squamocolumnar junction, followed by endothermic resection and dessication. "Localized hyperplasia of the squamous epithelium lining the cervix; fibrosis."

Comment: "There is not enough in this cervix at this time to make a diagnosis of malignancy. It is believed that the entire lesion was removed at the initial biopsy" (when diagnosis of carcinoma *in situ* was made) (Bucher).

Follow-up: Normal-appearing cervix; the patient moved from city and reports herself well. We have had some difficulty in tracing her but she is to return in May, 1950, for examination. (Since reciting this report, the patient was seen by me on May 26, 1950. She is symptomless and pelvic examination is essentially negative as is the Papanicolaou smear.)

DR. EMIL NOVAK, Baltimore, Md.—This question of the hormonal response of the cervical epithelium to pregnancy is an extension of the problem of the cyclic hormonal response of the cervical epithelium. It is curious that a cycle in the cervical epithelium has not yet been definitely worked out. There have been only three studies on the nedo-cervix from this standpoint, those of Wollner, Sjövall, and Topkins, with contradictory findings. A cycle in the stratified squamous portion has not been demonstrated, nor has there been any direct study on this point. For some time I have been collecting this epithelium by routine surface scrapings from the cervix. My primary purpose was to determine whether some of the basal-cell activity which has been stressed by some as a precursor of carcinoma could not be of cyclic hormonal nature, and I believe this to be the case. We have now gone far enough with the work to be impressed with the marked individual variations in tissue response.

As a matter of fact, we would expect the cycle in the squamous epithelium to be like that in the vagina because the two epithelia are continuous, but a definite histologic cycle has not been clearly demonstrable even in the case of the vaginal mucosa, although everyone recognizes its hormonal sensitivity. It may be equally difficult to establish a definite cycle in the cervical squamous epithelium. I believe we have gone far enough in our work to feel that many of the evidences of minor cell hyperactivity, and in the case of pregnancy sometimes very marked hyperactivity, are hormonal responses. As Dr. Te Linde and Dr. Danforth have mentioned, some at least of these changes are reversible. I have seen some of Dr. Hellman's cases and have been impressed with the fact that some of these pregnancy changes are reversible and apparently melt away after pregnancy. There are also cases in the literature of similar reversibility of marked cervical cell atypia in nonpregnant women, suggesting their probable hormonal causation, and thus putting us on our guard, particularly in the interpretation of the pregnancy pictures.

DR. TASSILO ANTOINE, Vienna, Austria.—We approached this problem in another way by looking at the living cell with an instrument which enables us to watch the living cervix *in situ*. The pictures we got were similar to those of Dr. Danforth but the cells did not stain as well as those of the nonpregnant cervix. However, we do feel that by means of this method we have determined that the differences between the pregnant and nonpregnant cervix are not very great.

FETAL MORTALITY*

L. A. CALKINS, M.D., PH.D., KANSAS CITY, KANSAS

(From the Department of Obstetrics and Gynecology, University of Kansas Medical Center)

AS RECENTLY as 1947, Mengert stated that "Approximately four per cent of all fetuses and newborn children reaching a size and development compatible with extrauterine existence die before, during, or soon after birth."¹ More recently, Edith Potter stated that, at the Chicago Lying-in Hospital, this fetal wastage had been markedly decreased in some categories, due at least in part, in her opinion, to an increased knowledge of fetal and placental pathology. Last year, before the American Medical Association, E. Stewart Taylor² pointed out the very much higher premature mortality in cases where the mother had a major pregnancy complication. This statement seemed so obvious to obstetricians that it was very surprising to hear the contrary opinion expressed by other students of fetal mortality. At the same meeting, Masters and Ross³ demonstrated that, at the St. Louis Maternity Hospital, it had been possible to reduce materially premature, intranatal, and postnatal mortality by the use of conduction anesthesia. Franklin F. Snyder⁴ has quite conclusively shown that most obstetric analgesia and anesthesia now employed is fraught with considerable danger so far as the respiratory function of the fetus, both during and following labor, is concerned. If we except gross anomalies inconsistent with life and gross intracranial injury, the vast majority of deaths intranatally and postnatally are associated with pulmonary dysfunction or pulmonary disease. Miller⁵ has recently pointed out the very great importance of hyaline membrane in the lungs, particularly in premature infants.

It seems quite clear, therefore, that a very great but as yet undeveloped, opportunity exists for the reduction of fetal wastage much beyond that realized today. Both Mengert and Taylor stressed the importance of dietary and economic influences, which, when adverse, seemed to increase fetal mortality. Mengert, in support of his contention, pointed to the much higher loss in the Negro race. Whether or not one would be able successfully to combat dietary deficiencies might be open to question, but it would seem highly unlikely that economic deficiencies could be corrected overnight. It is, however, possible to approach this problem from its many other angles in a constructive fashion. A review and analysis of 5,604 consecutive deliveries at the University of Kansas Medical Center[†] would indicate that the contentions of all of the above-named authors except one (Masters and Ross) can probably substantiated.

*Read at the Seventy-Third Annual Meeting of the American Gynecological Society held at White Sulphur Springs, W. Va., May 11 to 13, 1950.

†There were 50 antepartum, 27 intrapartum, and 77 neonatal deaths in these 5,604 consecutive cases for a gross wastage of 2.7 per cent.

We do not yet have sufficient information on conduction anesthesia to know whether it is as valuable as these authors contend. We are quite willing to accept their contention until it is proved otherwise.

TABLE I. FETAL AND NEWLY BORN MORTALITY, LATE TOXEMIA

	ANTE PARTUM	INTRA PARTUM	POST PARTUM	TOTAL	PER CENT
43 Premature	8	0	4*	12	28
103 Term	1	1	0	2	2

The 9 antepartum deaths:

No prenatal care, 4 (2 eclampsia, 2 nonconvulsive)

*All under 1,500 grams.

TABLE II. FETAL AND NEWLY BORN MORTALITY, PREMATURE SEPARATION

	ANTE PARTUM	INTRA PARTUM	POST PARTUM	TOTAL	PER CENT
19 Premature	7	1 (P)	2*	10	53
22 Term pregnancy	3	1 (P)	0	4	18

(P) Preventable.

*Both under 1,500 grams.

TABLE III. FETAL AND NEWLY BORN MORTALITY, DIABETES*

	ANTE PARTUM	INTRA PARTUM	POST PARTUM	TOTAL	PER CENT
4 Premature	1	0	1	2	50
12 Term pregnancy	1	0	1	2	16

*Other mortalities in diabetics assigned to toxemia or premature separation.

TABLE IV. FETAL AND NEWLY BORN MORTALITY, SYPHILIS

258 Patients, 7 Deaths = 2.7%
All ante partum (all Negro)
47 prematures, 3 deaths
211 term pregnancies, 4 deaths
3 no treatment (penicillin induction)
3 partial treatment
1 adequate? treatment

Tables I, II, III, and IV quite clearly show that the premature mortality associated with major obstetric complications is much greater than the mortality of those same complications when the baby is delivered at or near full term. In Tables V and VI, it will be noted that the etiology of antepartum and intrapartum deaths seemed sufficiently evident to the writer that "unknown etiology" needed to be resorted to relatively infrequently. In Table VII, the proportion of unknown etiology was much higher, particularly for those neonatal deaths in the premature group. While not all of these babies had been autopsied, the number so examined was well over 90 per cent. Each case had been carefully analyzed as soon as the infant began to do badly in the nursery. All factors concerning the pregnancy, labor, and subsequent nursery care were carefully scrutinized. Following death, this process was usually repeated. Not only were we interested in determining etiology, but we also wished to make all possible improvements in management before, during, and after birth. We were, therefore, quite concerned that as many as 23 out of 54 premature neonatal deaths had an unknown etiology. Whereas eight

of these infants weighed less than 1,000 grams and 14 of the 23 were under 1,500 grams, it nevertheless was not very satisfactory to have a pathology report of "prematurity," or even "atelectasis."

TABLE V. FETAL AND NEWLY BORN MORTALITY, ANTEPARTUM DEATHS

ETIOLOGY	530 prematures	31 deaths = 5.8%
	5,064 term pregnancies	19 deaths = 0.4%
Premature separation of placenta	7	3
Toxemia (convulsive and nonconvulsive)	8	1
Diabetes mellitus	1	1
Syphilis	3	4
Placental pathology	3	3
Prolapse of cord	1	1
Pneumonia	2	0
Erythroblastosis (?)	0	2
Gross anomalies	5	0
Unknown	1	4
Total	31	19

TABLE VI. FETAL AND NEWLY BORN MORTALITY, INTRAPARTUM DEATHS

	PREMATURE	TERM
Prolapse of cord	2	4
Birth trauma	0	6
Premature separation	1	1
Eclampsia	0	1
Placenta previa	2	0
Gross anomalies	1	1
Erythroblastosis	1	0
Fetal pneumonia	0	2
Unknown	2	3
Total	9 (1.18%)	18 (0.4%)

TABLE VII. FETAL AND NEWLY BORN MORTALITY, POSTPARTUM DEATHS

	PREMATURE	TERM
Gross Anomalies	4	4
Erythroblastosis	1	6
(P) Brain hemorrhage	6	0
(P) Prolapsed cord	1	2
(P) Fetal pneumonia	6	1
(P) Fetal, other infection	2*	2*
Toxemia	4†	0
Placenta previa	1†	0
Diabetes	1 (P)	2
Miscellaneous	5	2
Unknown	23	4
Total	54 (10.8%)	23 (0.4%)
1,000 gram	8	
1,001-1,495 gram	6	
1,500-1,995 gram	9	

(P) Preventable.

*Pediatric (?).

†All under 1,500 grams.

A complete reanalysis of the material, taking into account moderately intangible causes of asphyxia such as occult prolapse of the cord, which can rarely be diagnosed with certainty, resulted in a distribution of etiological factors such as that indicated in Table VIII, which still leaves ten premature and eleven term babies whose deaths were of unknown etiology. Dr. Herbert

C. Miller had analyzed this same material, with respect to the occurrence of hyaline membrane, and quite independently of our own efforts. Combining his study and our own, we found that, as indicated in Table IX, all ten of the premature and three of the full-term babies, whose deaths were previously of unknown etiology, had a marked degree of hyaline membrane present. While it is not yet known what proportion of infants with hyaline membrane will die, nor what degree of hyaline membrane is necessary to produce death, it seems quite clear that here we have a pathologic entity not previously recognized and yet one which is, in many instances at any rate, inconsistent with life. No doubt there are some other pathologic entities in fetuses which are not yet generally recognized, and quite certainly our knowledge of placental pathology is very deficient.

TABLE VIII. FETAL AND NEWLY BORN MORTALITY

	PREMATURE	TERM PREGNANCIES
Total losses	94 (17.7%)	60 (1.2%)
Cause unknown	10	11
Causes known	84	49
Premature separation placenta	31%	17%
Placenta previa		
Toxemia		
Diabetes		
Gross anomalies	15%	27%
Erythroblastosis		
Miscellaneous	28%	8%
Prolapse of cord	26%	49%
Brain hemorrhage and other trauma		
Fetal pneumonia and other infections		
Syphilis		

TABLE IX. FETAL AND NEWLY BORN MORTALITY

	PREMATURES	TERM PREGNANCIES
Total losses	94 (17.7%)	60 (1.2%)
Cause unknown	0	8
Causes known	94	52
Premature separation placenta	22%	12%
Placenta previa		
Toxemia		
Diabetes		
Gross anomalies	13%	21%
Erythroblastosis		
Hyaline membrane	24% (23)	15% (8)
Miscellaneous	20%	8%
Prolapse of cord	20%	44%
Brain hemorrhage and other trauma		
Fetal pneumonia and other infections		
Syphilis		

It would seem that there are three very distinct avenues of approach to a much lower fetal mortality in the future: (1) Improved obstetric care should bring about a reduced incidence of premature delivery. Cosgrove, Randall, and Johnson have all shown that placenta previa babies can, under certain limited circumstances without material risk to the mother, be delivered at a somewhat later period than was formerly thought possible. Improved prenatal care has materially reduced the incidence of eclampsia, and has stayed the advance of existent toxemia, so that fewer premature inductions are now necessary. While syphilis has not been eliminated as a cause of premature

still birth, material improvement has been brought about. (2) The management of labor still needs much improvement. Schreiber,⁶ Cole,⁷ Beck,⁸ Snyder, Mengert, and many others have warned against large dosages of analgesic and anesthetic drugs, and also against the use of multiple agents, and yet their use continues. Whether the answer is to be found in the simple conduction anesthesia, as recommended by Masters and Ross, or in the use of well-controlled nitrous oxide and oxygen analgesia and anesthesia, as routinely used at the University of Kansas Medical Center until very recently, or in some other relatively simple and relatively innocuous relief of pain, remains to be seen (Table X). A more clear-cut understanding of the indications for and optimum time of performance of the various types of operative delivery will almost certainly bring about a marked reduction in fetal loss. (3) It is recognized that most macerated fetuses and some nonmacerated fetuses presented to the pathologist show so much autolysis of tissues that accurate analysis of the pathologic condition present, previous to death, is impossible. This has no doubt led to an attitude of mind among many pathologists that it is more or less useless to study dead fetuses carefully. That such an attitude is not justifiable has now been amply proved by the work of Edith Potter, Herbert Miller, and others. It is also quite obvious that our knowledge of placental pathology could be very greatly increased.

TABLE X. PREMATURE MORTALITY IN FETUSES ALIVE AT ONSET OF LABOR

WT. IN GRAMS	MASTERS AND ROSS	KANSAS
500-1,000	33-30-91%	18-13-72%
1,000-1,500	62-25-40%	39-16-41%
1,500-2,000	140-21-15%	108-19-18%
2,000-2,500	356-22-6%	334-15-4%
Total	591-98-16.6%	499-63-12.6%
	Nonconduction anesthesia (347) = 20.8%	Only a very few of these had conduction anesthesia.
	Conduction anesthesia (244) = 10.7%	

It would seem a simple matter to bring about improvement in all three of these categories by the simple expedient of organizing "Fetal Welfare Committees" along the lines of the Maternal Welfare Committees of the past two decades. Each fetal death should be analyzed with the same care that maternal deaths have been analyzed. Etiology should be carefully investigated; patient and physician responsibility should be established; pathologists should be encouraged to do more careful autopsies and to search for possible new pathologic entities. For such committees to be effective, the combined efforts of obstetrician, pediatrician, and pathologist will be required. In some instances, a contribution can be made by the pharmacologist and physiologist. The project is not forbidding. It can, as a matter of fact, be rather easily carried out. We have, just recently, at the University of Kansas Medical School, employed such conferences as a teaching exercise for the senior students. Up to date, they have exhibited the same live interest in these conferences that they have in the Clinical Pathological Conferences so long employed in the case of adult deaths. It is hereby recommended that the American Gynecological Society sponsor the organization of Fetal Welfare Committees.

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Discussion

DR. PHILIP F. WILLIAMS, Philadelphia, Pa.—In 1946, there were, according to the figures of the National Office of Vital Statistics, 153,928 stillbirths and neonatal deaths, and, if we add the estimated abortions, approximately 150 of each 1,000 conceptions, that year, did not reach the end of the first month of extrauterine life. To diminish this great wastage in reproduction is, at the present time, one of the most important tasks in preventive medicine.

Dr. Calkins has listed the major etiological factors of stillbirths and neonatal deaths. Certainly the incidence of many of these causes can be reduced. Improved prenatal care, study, and treatment should serve to avoid or ameliorate some major complications and carry a certain proportion of fetuses in such instances to viability. Particularly in one factor the essayist mentions, nutrition, Burke and others have shown the indubitable effect of poor maternal nutrition on the outcome of the fetus. Labor can still be benefited by improvement in judgment and technique in operative delivery. The use of diethylstilbestrol as a prophylactic against a number of obstetrical complications is gaining ground. Its success in preventing the development of toxemia in diabetes should stimulate its further use in toxemias in nondiabetic women.

The group of deaths usually listed as due to unknown causes, macerated fetus, or just prematurity, will lessen as the importance of early and competent pathologic examination is recognized, with full histologic study of the various organs.

A fundamental problem for study in this connection is the elucidation of the factors which cause premature rupture of the membranes, a most frequent etiological factor in producing premature labor, and a potent influence in producing intrapartum infection in the term infant.

The author's findings based upon Miller's analysis of the same material as to the occurrence of hyaline membrane, with an almost complete explanation of the group of deaths from unknown causes are interesting. It may be mentioned that Miller found this fibrinoid material lining the alveoli, in the bronchioles and alveolar ducts, in cases of neonatal death, and regards its presence as a result of some injury to the epithelium and walls of the terminal air spaces. The nature of the injury he has not determined, but the lesion appears to resemble closely that seen in individuals dying of pandemic influenza. In such cases, the mother was usually free of major obstetric complications and the infant was born alive prematurely, to die within forty-eight hours of marked respiratory difficulty. Miller feels that the agent which causes the fetal pulmonary injury also precipitates labor and birth. Maternal protein deficiency, as well as unknown infection, is the speculative etiology.

Fetal, stillbirth, and neonatal mortality committees in Philadelphia have functioned for over ten years. They are set up exactly on the pattern of the Maternal Mortality Committee. At present, due to a paucity of maternal deaths in Philadelphia, the Neonatal Mortality Committee occupies the limelight at the now joint meetings.

It is perfectly clear that all stillbirths occur under the care of the obstetrician, and the genesis of fully half the neonatal deaths occurs during labor. Hence, I heartily endorse Dr. Calkins' proposal that obstetricians should initiate widespread formation of Fetal Welfare Committees.

DR. M. EDWARD DAVIS, Chicago, Ill.—Dr. Calkins' discussion of fetal mortality is timely and pertinent. The continued and spectacular decrease in maternal mortality in

the United States has focused attention on the problem of fetal mortality. The same concerted efforts which have been directed toward the improvement of maternal mortality, applied to the equally important problem of fetal deaths, should yield equally good results.

At the Chicago Lying-in Hospital the total mortality of infants weighing 1,000 grams or more has decreased rather precipitously during the last 10 years, reaching a low of 20 per 1,000 births in 1948 and 21 in 1949. This mortality has been divided almost equally between live births and stillbirths during the last year. There has been a steady decrease in the mortality of liveborn infants weighing 1,000 to 2,500 grams, which reached the low figure of 10 per cent in 1949. The incidence of this group has remained rather constant at 6 per cent of the total births. The mortality of living babies weighing more than 2,500 grams has remained unchanged at about 0.5 per cent.

The pattern of neonatal mortality has changed markedly in this last decade. Deaths from trauma, anoxia, and infection have decreased markedly. There has been no great change in the number of neonatal deaths due to malformations and erythroblastosis. The most important cause of death in the newborn is pulmonary disease, which accounts for 4.9 deaths per 1,000 live births in babies weighing more than 1,000 grams, almost half of the total neonatal mortality of 11.4 during the years 1946 to 1948. When one breaks down the causes of fetal deaths during 1939 to 1949 it is astonishing that it accounts for 57.2 per cent of all premature deaths.

Dr. Edith Potter in our clinic has been interested in this large group of babies who die of pulmonary disease. She has been particularly impressed with a clinical entity which for want of a better term is labeled as "resorption atelectasis." It is this condition which I wish to bring to your attention particularly.

In the typical case, the baby is delivered by cesarean section, perhaps somewhat prematurely. At birth he begins to breathe spontaneously and soon cries lustily. At abdominal delivery under regional anesthesia the baby may cry before he has been removed completely from the uterus. Within a short time, rarely later than several hours after delivery, the baby will develop increasing respiratory difficulty exhibited by marked retraction of the chest, increasing cyanosis, and will expire within 24 to 72 hours after delivery. If he lives for a longer period he will usually develop pneumonia. At pathologic examination the characteristic findings are an increased amount of intracranial fluid and a hyaline-like, eosin-staining membrane surrounding most of the alveolar air sacs.

Apparently, the development of this condition is favored by prematurity and abdominal delivery. It is extremely rare in the baby weighing more than 2,500 grams delivered naturally. In 1,181 cesarean sections at the Chicago Lying-in Hospital in the period 1942 to 1948, there were 56 fetal deaths. If malformations and erythroblastosis are excluded, all the other babies succumbed to "resorption atelectasis" with two exceptions, one weighing 1,060 grams. These data bring into sharp focus the fact that nonpreventable fetal death is the one real hazard in cesarean section today. Potter and our pediatric staff have carried out many clinical and laboratory experiments on the mechanism by which eosin-staining, granular, hyaline-like material slowly deposits on the inside of the pulmonary alveoli during the early hours of extrauterine life, slowly shutting off the newborn's oxygen

TABLE I. CHICAGO LYING-IN HOSPITAL 1939-49. CAUSES OF PREMATURE DEATH

	1,000-1,499 GRAMS	1,500-1,999 GRAMS	2,000-2,499 GRAMS	TOTAL %
Trauma	2	7	5	5.6
Anoxia	8	6	4	7.0
Malformations	13	14	16	18.8
Erythroblastosis	1	2	8	4.4
Pulmonary disease	74	46	23	57.2
Hyaline membrane	40	29	16	34.0
Hemorrhagic pneumonia	14	8	2	9.6
Pneumonia	20	9	5	13.4
Other	2	1	1	1.6
No pathologic abnormalities	11	3	0	5.6

TABLE II. CAUSES OF NEONATAL MORTALITY IN CESAREAN SECTION, 1,181 DELIVERIES, MARCH, 1942, TO APRIL, 1948

	PREMATURE	TERM	TOTAL
Malformations	2	5	7
Erythroblastosis	2	5	7
Increased intracranial fluid, hyaline membrane	22	9	31
Pneumonia	2		2
Pulmonary hemorrhage and asphyxia	3	4	7
No abnormality, premature (1,060 grams)	1		1
No autopsy		1	1
Total	32	24	56

TABLE III. NEONATAL MORTALITY PER 1,000 LIVE BIRTHS OVER 1,000 GRAMS

	1931-41	1941-46	1946-48
Trauma	3.4	1.0	0.2
Anoxia	2.5	1.0	0.5
Malformations	2.3	2.9	3.5
Infections	1.5	1.0	0.9
Erythroblastosis	0.6	1.5	1.0
Increased intracranial fluid	0.6	1.0	0.4
Pulmonary pathologic conditions			
Term	2.4	0.9	0.7
Premature	4.2	3.2	4.2
Total	17.5	12.5	11.4

supply, but they have been unable to provide any real clue. The various suggestions as to its prevention and therapy have not decreased the likelihood of this fetal complication. Intensive research should be directed to unraveling the cause of this important fetal hazard.

SIR EARDLEY HOLLAND, London, England.—As Dr. Calkins and Dr. Davis have pointed out, fetal mortality is one of the most important public health problems in medicine. The status of the fetus has become much more important since pregnancies have been spaced and limited, as has occurred in all social classes during the last twenty-five years. We in Britain are much more interested in *why* the fetus dies than in *how*. Fetal pathology will show *how* but it does not necessarily show *why*.

Let me take a hypothetical case. A stillborn premature baby is found to have cerebral hemorrhage. That is *how* it died. But why was it born prematurely? In Britain we have worked out the association between premature labor and social and economic conditions; we know that premature labor is twice as frequent in the lower than in the upper social classes.

In Britain there was a remarkable fall in fetal mortality during the war. This fall may have been due to the more even distribution of essential foods by rationing, and to the priorities granted to pregnant women for milk, eggs, and butter, and the free distribution of vitamin concentrates. But diet cannot have been the only reason, for the fall was even greater in the upper than in the lower social classes. There was also improved obstetric care, owing to evacuation of the pregnant women from big towns into well-staffed emergency maternity homes in country districts.

It seems to me that the two most important means of preventing fetal death and premature labor are to insure that the population of a country has good health and physique, and that means, among other things, good standards of diet, housing, and education. The other great preventive measure is a good standard of obstetric care. It has been shown that in the poorer social classes, no matter how good the obstetric care, the fetal mortality cannot be brought down to the level of that of the upper classes. I think the reason why the fetal mortality is so low in Denmark and Holland and Sweden is that the population of those countries is homogenous or uniracial and is healthy. Those countries are not

highly industrialized; the people live largely in the country and eat an abundance of their own good food; their standards of education and of their general medical and obstetric services have for many years been very high.

DR. CALKINS (Closing).—Dr. Gordon Douglas could have reported the same findings as Dr. Davis has—20 deaths per 1,000, and my own figure was about that. I would have to differ with Dr. Davis in one item only. He pointed out that these hyaline membrane cases were likely to be found in babies delivered by cesarean section. I must repeat what Dr. Williams has said about Miller's experience. It occurs almost exclusively in women who had absolutely no abnormality whatever in their pregnancies or in their labors. The babies are fine at birth but dead within twenty-four to seventy-two hours. In other words, there is no excuse for doing a cesarean section. They are perfectly normal individuals. I think if we went away with the idea that cesarean section might produce this lesion we would have the wrong impression.

THE PLACE OF RADIOACTIVE ISOTOPES IN THERAPY*

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IT IS probably not appropriate to talk with any finality about the place of radioactive isotopes in therapy. It probably will be inappropriate to talk about this for some years. Therefore, if by any chance in the course of the words which I am about to speak anything comes out regarding the ultimate place of radioactive isotopes in therapy, it will be merely a projection of the present situation into the unknown.

I think we have criteria which are of some value in enabling us to guess what the radioactive isotopes will have to offer. Progress in the field will be due to the patience and ingenuity of clinical men using isotopes and to the imagination of research men seeking information which may be of assistance in envisioning their possible uses. Radioisotopes, we can say categorically, are useful by virtue of the radiation which they give off. Their ionizing radiation may be used in therapy as one uses x-rays, radium γ rays, or some of the newer types of accelerators. Isotopes may also be useful in various diagnostic procedures, although radioisotopes are not likely to supplant radiographic apparatus except in such fields as metallography. In certain instances it is possible to measure movement of material within the body, as by injecting or ingesting radiosodium,¹ taking advantage of the fact that radiation can be measured and partly localized by instruments outside the body, where γ rays are involved. The fate of radioiodine gives information as to thyroid function which is in some cases superior to that obtained otherwise. The isotopes have been useful and will be increasingly useful in the types of diagnostic procedures that have employed dyes, as for example plasma and red-cell volumes.² By using isotopes of elements that are present normally in the body it is possible to measure the volume of these materials. This is possible with sodium or potassium because essentially all of the sodium or potassium in the body exchanges with its introduced isotope in a short time; thus, within an hour or two, the concentration in blood of an injected sample of the radioisotope gives us by calculation of the volume of dilution, the amount of the electrolyte in the body or at least a figure which is closely related to it.³

Passing to the more basic aspects of physiology and biochemistry we find the field of investigation in which radioactive elements have been most fruitfully used up to the present time. This is especially true of the tracer method as used in studying pathways of metabolism and the fate of substances, chemical groups, and atoms which are introduced into the body. Since Schoenheimer⁴ first laid emphasis on the dynamic state of body constituents and on the use of tracer

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methods, a drastic revision of our concepts in physiological chemistry has been taking place. If we may trust the history of clinical research, these techniques will be used in the clinic, perhaps routinely, in the near future; this is retarded chiefly through our present uncertain state regarding the human toxicity of several isotopes, notably carbon¹⁴. Of particular interest to gynecologists will be the metabolism of the steroid hormones. They may be produced by chemical synthesis, in which case certain groups will bear a carbon¹⁴ label, and we are investigating the possibility of manufacturing "indiscriminately" labelled steroids by biosynthesis. Plants grown in an atmosphere containing C¹⁴O₂ will contain a large variety of labelled components, including plant steroids. By using the plants as fodder for animals, similarly labelled animal constituents will be obtained. Whether chemical synthesis or biosynthesis will be more efficient or suitable for various purposes depends on many factors, including the efficiency of the synthesis and the nature of the problem to be investigated.

There are various means of approach to the therapy of pathologic states, taking advantage of radioisotopes. We may now, with this cursory discussion of diagnostic and research potentialities, consider the essentials of the problem which we are trying to elucidate this evening. What means of approach are there to therapy of human disease with radioactive isotopes?

Radiocobalt (cobalt⁶⁰) has been found useful as an external radiation source or in interstitial therapy, in which cases it is used essentially as a radium substitute. Dr. Barnes will discuss the use of radiocobalt in treatment of carcinoma of the cervix in this program. This is pioneer work because, despite our experience with radium in the therapy of malignant disease, cobalt⁶⁰ has a homogeneous gamma radiation of different energy, so that a considerable amount of exploratory work must be done over again. Successful interstitial therapy depends, after all, on a proper relation between dosages to tumor and normal tissues; in therapy of lesions of the cervix these factors are both clear-cut and critical. This painstaking work is therefore important in setting the standards of cobalt⁶⁰ therapy in general. This isotope has the advantage over radium in that there is a much greater potential supply and a potentially greater specific activity.

It is also possible to localize radioactivity by injecting an insoluble radioactive material rather than by insertion of needles or other fixed sources. Injection of radioactive material into malignant tumors has not been generally employed. The variables in obtaining localization are considerable, and no great effort has been put into this. Some insoluble compounds of well-known isotopes have been used in colloidal form as injection solutions. Suspensions of chromium phosphate containing radioactive phosphorus have been injected into and infiltrated around tumors with expected results.⁵ It has been hoped that suspended or colloidal radioactive substances might be carried through the lymphatics to those lymph nodes that drain the tumor. This has not been proved to take place to an extent which results in a useful degree of irradiation of a potentially metastatic area. Thought should perhaps be given to some other technique, biologic or chemical, which might accomplish this purpose.

Very few injected isotopes—sodium being the most noteworthy exception—result in diffusely distributed irradiation. The most remarkable example of localization of an isotope is the case of iodine, which concentrates in the thyroid gland for physiological reasons. Bone concentrates radiocalcium similarly. There are other cases in which organs concentrate certain elements although they are not apparently actively using these elements, as in the case of concentration of gallium and the rare earths in bone. Strontium, barium, and radium are deposited in the skeleton since they may substitute for calcium in the structure.

In some cases active storage does not occur, but tissues containing a high concentration of a natural element will concentrate the isotope due to exchange between the radioactive and nonradioactive atoms, as with phosphorus, so that a high concentration of any substance makes one suspect (but does not establish) that the corresponding radioactive element will concentrate there. Some areas, like the brain, are metabolically relatively inert, due largely to the blood-brain barrier. On this basis brain tumors may be localized by injection of certain substances which will not necessarily concentrate in the brain tumor more than they would in, for example, muscle, but will avoid the normal cerebral tissue. This avoidance of a tumor is obviously the reverse of useful in therapy, but has realized diagnostic value. Some isotopes or compounds are concentrated more actively in organs which are actively growing, or they may be taken into growing organs and may fail to exchange in the opposite direction after they are synthesized into relatively stable compounds. For instance, an adult animal inhaling radioactive carbon dioxide disposes of 99.9 per cent of the radioactive carbon within a few days. But if an embryo is exposed shortly before term through the mother's circulation, although it stores a relatively small amount of the radioactive carbon, the greater part of the stored C¹⁴ is held in the tissue for a long period of time while the fetus is growing up. In this case, of course, the isotope is diluted by new tissue which the animal produces in the course of growing so that the irradiation dose diminishes as the animal approaches maturity.⁶ In a similar way, radiocarbon, laid down in hair, appears to remain there.

Radioactive elements may be used by virtue of their deposition as colloids. I have mentioned their local use. If colloids of suitable particle size are administered intravenously they will tend to show a certain pattern of concentration that varies with the size of the particle; thus it is possible to get the bulk of radioactive colloid in the lung, liver, or spleen. This has been used in therapy for the purpose of directing therapy particularly to the liver or spleen. Many tumors are infiltrated by cells of reticuloendothelial origin which tend to take up radiocolloids just as they do certain dyes.⁷ However, tumor concentration of colloids has not been especially favorable; in general, the tumor concentration here is less than it is in liver or spleen.

Generally speaking, the "total-body" treatment of tumors and their metastases represents the philosopher's stone in isotope therapy, which we are seeking without assurance of attainment. The most encouraging instance, that of iodine therapy of thyroid carcinoma, does not necessarily forecast other solutions based

on the same principle. Despite the high relative concentration of iodine in the normal thyroid (1,000-fold the average concentration in other tissues) only a few thyroid neoplasms take up useful amounts of the isotope, and it has often been necessary to approach total-body radiotoxic levels to gain a response even in these cases. The fact that tumors may be conditioned to take up I^{131} after destruction of the normal gland, probably through mediation of the hypophysis, suggests a principle that may be useful elsewhere.⁸

Although many isotopes concentrate in bone, especially in growing osteogenic tissue, attempts to treat osteogenic tumors by this principle have not been successful due to the radiotoxicity to normal bone and to bone marrow which goes along with the requirement for a tumor dose. It will be necessary to look for metabolic characteristics of a particular tumor cell type (for example, plasma-cell myeloma).

Beyond this there may, of course, be some metabolic peculiarity of tumors in general. No basic metabolic disorder of tumor tissue is well understood, but the characteristic biologic behavior of neoplasms suggests that there may be a common chemical basis. If this were to be, for example, a special enzyme pattern which caused the accumulation or breakdown of certain compounds or was associated with a particular behavior of an inorganic element, this might lead to a general solution in the therapy of metastasizing tumors. The basic peculiarity might be discovered by biochemical research or such an agent might be discovered by purely empirical means.

I shall mention the present clinical indications in so far as they can be covered briefly. Radioactive phosphorus is probably the most widely used agent. It has a rather interesting distribution in the body. It is found to be most concentrated in rapidly growing tissue and cells of the blood-forming organs and bone. It has therefore been very useful in the treatment of leucemia and allied disorders, and occasionally in rapidly growing radiosensitive tumors of other types. The disadvantage in the use of any agent which has a factor of concentration in blood-forming organs is that these are among the most radiosensitive tissues in the body and, in fact, limit the amount of general body radiation which can be given. In the final analysis, therefore, despite the usefulness of P^{32} , it seems fair to say that P^{32} is not an agent which is absolutely indicated in therapy, since one may use, alternatively, total-body or local irradiation or chemotherapeutic agents. There are other isotopes which fall into the same category: radioactive sodium and arsenic. We have used radioactive arsenic in collaboration with the clinics at the University of Chicago. Although it has proved to be effective as a substitute for total-body radiation, it is difficult to prepare, and has no probable advantages in therapy.⁹ The possibility remains, of course, that this or any other agent might turn out to be unexpectedly valuable in the therapy of some particular tumor type. Iodine¹³¹ has been used in thyroid therapy and although it is effective only in occasional cases of carcinoma, it probably represents the one instance where a given isotope is absolutely indicated in cancer therapy, since (where it is effective) it has no substitute. In working

out iodine therapy for carcinoma, the large dosage calls attention to the biologic side effects, since the incidental total-body radiation may approach the lethal dosage occurring in atomic bomb casualties.

It is hoped that compounds of carbon¹⁴ will come into use because of the variety of possible compounds which might be useful for special purposes. Drs. Geiling and Scully have been extracting drugs from plants exposed to radioactive carbon dioxide.¹⁰ By chemical synthesis, one can obtain compounds with only one labelled carbon atom. These are especially interesting to the biochemist; possibly in therapy we will become interested in labelling as many carbon atoms as possible.

I would like to say a word about tritium which emits a very weak beta ray (5.7 kilovolts). Being an isotope of hydrogen it, too, may be synthesized into organic compounds generally. Its virtue lies in the fact that radiation can potentially be localized on the cytological level, near the source. The range of the beta ray is 2 microns, or less than the nucleus of the cell. This isotope has been used in human beings for body-water determinations,¹¹ but is untried clinically.

I should certainly not want to conclude without making one or two remarks about a subject which must be of interest to this group. What might be the possibility of producing radiation damage to the germ plasm of the developing embryo by administering isotopes in pregnancy? The problem is essentially similar to that raised in connection with irradiation by x-ray of the pelvis containing a growing fetus. Presumably, the same rules should apply as in diagnostic radiography, and with associated experimental work it should be possible to estimate the dosage to the fetus and to the gonads which would follow radio-isotope administration. Recent work has shown¹² that 200 to 400 r x-ray induce effects on the fetus which depend on its stage of development. In the earliest embryos, the damage results in abortion; in later stages malformed embryos develop to term. These stages (judging by the developmental picture in experimental mice) correspond to very early pregnancy in the human being.

The medical future of radioactive isotopes will, at first, lie largely in the field of basic biochemical research and will be valuable in the understanding of such problems as growth, for which the cruder biochemical procedures have not been satisfactory but for which the tracer technique is ideally designed. Such investigations will have an impact on clinical practice. Recalling the lapse of time between discovery of the x-rays and examination of the Fallopian tubes by radiologic methods, one can see that the full development of the possibilities of a discovery, even in more or less obvious clinical application, takes time. But we may take assurance in the fact that clinical practice is becoming ever closer to basic experimental research.

Finally, in the therapy of disease, particularly carcinoma, there will exist for many years the possibility of discovering radioactive compounds with special affinity for carcinoma or for particular types of carcinoma. To be ideally effective, such compounds must exhibit affinity by factors of 100 or more above the total-body concentration.

A further possibility exists, at least in theory. Since the limiting factor in any form of general radiation therapy may be the ability of the total organism to withstand radiation effects, the prophylaxis and therapy of radiation toxicity itself might prove to be useful in enabling us to increase the total-body dosage. The therapy of radiation damage is, of course, increasingly important in the "atomic age." Symptomatic therapy by agents which neutralize heparin,¹³ or by the use of antibiotics¹⁴ and properly controlled transfusions, may not be expected to vitiate tumor therapy. On the other hand, prophylactic cysteine injection, while diminishing irradiation sickness,¹⁵ appears to protect tumors from irradiation, at least partially, as well.¹⁶ This may be expected to happen in the case of agents whose action is on the basic chemical or cytologic level.

At least it is safe to predict, through increasing use of isotopes in a variety of ways, a continuation and acceleration of the slow, steady progress which clinical medicine, surgery, and radiology have been making during the past few decades. I am sure radiation therapy will be in an even more satisfactory state ten years from now than it is now and it may, in the final analysis, be impossible to say exactly why.

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COAGULATION DEFECTS WITH INTRAUTERINE DEATH FROM Rh ISOSENSITIZATION*†

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STUDIES of the blood coagulation mechanism in pregnancy have indicated that incoagulable blood may be associated with occasional cases presenting certain obstetrical complications. This defect has been noted to occur in patients with severe premature separation of the placenta. The decrease in the clotting ability of the blood in these patients is associated with fibrinogenopenia, hypoprothrombinemia, and, on occasion, the presence of a circulating fibrinolysin.¹

Recently another group of patients have been recognized who may develop an abnormality in their coagulation mechanism as a complication of pregnancy. In 1946, a patient‡ who was Rh negative, had anti-Rh agglutinins, and in whom the fetus was known to have been dead for several weeks, was admitted to the Boston Lying-in Hospital as an emergency case in early labor. On examination it was noted that the patient had several recent ecchymotic areas of the skin. Her subsequent clinical course was complicated by intrapartum and postpartum hemorrhage. The findings and clinical course of this patient posed the question whether a coagulation defect might have been present in this case. Studies of the blood coagulation mechanism were not done, but whatever factors contributed to the hemorrhage appeared to be overcome by multiple transfusion. To investigate the problem further, the blood of other patients with a similar clinical condition has been studied. During the past two years fifteen Rh-negative patients who had anti-Rh agglutinins with intrauterine death presumable on the basis of this isosensitization have been studied. In all cases the fetuses were retained in utero for various periods after death. The components of the coagulation mechanism were normal in twelve of these patients and the amount of blood lost at the time of delivery was not unusual. However, in the remaining three patients, marked defects in the coagulation mechanism could be demonstrated and it is this group that forms the basis of this communication.

Methods and Material

Methods of measuring the components of the clotting reaction have been detailed in a previous publication.¹ In brief, these included clotting tests, tests for fibrinolytic activity and possible presence of anticoagulants, platelet counts, prothrombin activity determinations, and the blood concentration of fibrinogen. These studies were made on the following patients:

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‡This patient is included with the kind permission of Dr. Paul Gustafson.

The first patient observed with this condition was Mrs. D, 36 years of age, gravida vi, para iii, Rh negative, whose expected date of confinement was Oct. 23, 1948. During the fifth month of pregnancy an increase of the anti-Rh titer to a level of 64 was found and at this time death of the fetus occurred. Her past obstetrical history included two normal pregnancies in 1941 and 1943, but in 1944 a stillborn erythroblastotic infant was delivered. During 1947 the patient had two early miscarriages. On September 30, in the ninth month of this pregnancy and ten weeks after intrauterine death, blood samples were taken for study of the coagulation mechanism. The clotting time was 6 minutes and the clot that formed was large and stable after 24 hours of incubation. Ten days after these observations the patient had a few labor pains while at home and shortly thereafter delivered precipitously the products of conception. Directly thereafter she started to bleed and continued to bleed profusely during the 20 minutes required to reach the hospital.

Physical examination on entrance showed a pale woman in severe shock with a weak pulse of 100 beats per minute and a blood pressure of 70/40. There was a liquid blood loss in the blankets estimated at 1,200 c.c. and clotting was absent. Purpuric or ecchymotic areas on the body were not observed. The uterus appeared well contracted and in spite of additional oxytocic drugs, there was a steady escape from the vagina of bright red blood which failed to clot. The clotting time was 1 minute and the bleeding time 3 minutes. However, the clot that formed began to fragment within 30 minutes and was completely dissolved within one hour at room temperature.

Transfusions of Rh-negative blood were immediately administered on entrance to the hospital. One thousand c.c. of blood were given during the first half hour, to which were added 500 mg. of vitamin C and 15 mg. of vitamin K. Nevertheless, blood which still failed to clot continued to trickle from the vagina. Examination of the products of conception revealed a macerated fetus in an intact ovisac, thus ruling out retained placental tissue as a possible cause of the bleeding.

Within four hours after entrance, 3,000 mg. of fibrinogen* and an additional 3,000 c.c. of blood were administered. The blood pressure rose to 100/70 and the pulse decreased to 80 beats per minute. However, vaginal bleeding continued from the well-contracted uterus, although in noticeably diminished amounts following the fibrinogen administration. Because of the continued bleeding the patient was examined five hours after admission in the operating room with preparation for laparotomy. Nothing was found to explain the bleeding but removal of the exploring hand from the uterine cavity was followed by a gush of 500 c.c. of blood. The uterus was packed but the patient immediately bled through the pack. A subtotal hysterectomy was performed with the patient receiving an additional 2,000 c.c. of freshly drawn blood. The patient withstood the procedure well and did not exhibit any bleeding tendency during or after hysterectomy. Venous blood drawn from the patient directly after operation clotted in 10 minutes. The clot that formed was large in size and remained stable after 24 hours' observation. Recalcification of the patient's plasma produced a good fibrin clot, indicating the presence of adequate fibrinogen. The uterus was normal on pathologic examination.

The day after operation the patient's hemoglobin was 57 per cent, the prothrombin activity 100 per cent, the red count 3.6 million, and the bleeding time 2½ minutes. The hemoglobin was 38 per cent on the fifth postoperative day and the patient was given an additional 1,000 c.c. of blood. On the eleventh postoperative day the blood fibrinogen was 210 mg. per cent and three months after delivery the blood clotting and blood fibrinogen values were normal.

The second patient was Mrs. S., 31 years of age, gravida viii, para v, Rh negative, whose expected date of confinement was Oct. 22, 1948. Her past obstetrical history revealed that only her first child is alive and well. At least three of the remaining infants were known to have had erythroblastosis and were stillborn. Her prenatal course was complicated by an increasing titer of Rh antibodies to 64 during the middle trimester.

*The human fibrinogen used in this study was kindly supplied by the Medical Director of the National Blood Program and was processed by the American National Red Cross from blood which it collected from voluntary donors.

Intrauterine death occurred during the sixth month of pregnancy. The patient was admitted one month from term because of vaginal bleeding and intermittent cramps of five hours' duration. Physical examination showed an extremely anxious patient who was bleeding moderately from the vagina with each uterine contraction. The blood pressure was 114/80, the pulse was 80. There were several ecchymotic areas over the thighs and legs. The uterus was soft and consistent with a six months' pregnancy.

On entrance the clotting time was 15 minutes. This clot became markedly fragmented within 15 minutes after its formation, leaving the blood completely fluid. The plasma fibrinogen concentration was 30 mg. per cent. A circulating fibrinolysin could not be demonstrated in the patient's blood. The level of antifibrinolysin was elevated. The platelet count was 150,000 and the prothrombin activity 50 per cent.

Five hours after entrance the patient delivered a stillborn, macerated fetus, together with a complete ovisac. This was followed immediately by 200 c.c. of unclotted blood. The uterus contracted well.

The intravenous administration of fibrinogen was started at the time of delivery and 3,000 mg. were given during the first half-hour after delivery. During the first 15 minutes after delivery, an additional 300 c.c. of blood were lost by vaginal trickle and this blood did not clot. However, at the completion of the administration of fibrinogen, an occasional clot appeared at the vulva and uterine hemostasis was satisfactory. A venous blood sample taken at this time showed a normal-sized clot with no evidence of clot dissolution after 24 hours of incubation. Blood studies on the first postpartum day showed a clotting time of 2 minutes, a blood fibrinogen of 200 mg. per cent, a platelet count of 150,000, and a prothrombin activity of 100 per cent. The patient was discharged well on the eighth postpartum day. Subsequent studies revealed her coagulation mechanism to be normal. Three months after delivery the patient had hepatitis which was thought to be caused by a virus contaminant in the fibrinogen solutions. (Since this time, only specially prepared fibrinogen, treated with nitrogen mustard which is then neutralized, has been supplied by the American Red Cross and obviates the danger of homologous serum jaundice.)

The third patient, Mrs. R., was a 26-year-old gravida iv, para iii, Rh negative, whose expected date of confinement was Jan. 15, 1950. Her past obstetrical history revealed that two children were normal but the third child had erythroblastosis from which he recovered. By the sixth month of the fourth gestation the anti-Rh titer had risen to 256 and intrauterine death of the fetus occurred at that time. In the month prior to the intrauterine death, the patient had a sudden weight gain of 8½ pounds, a small amount of albuminuria, and transient pyuria. The blood pressure was normal. The patient lost 6 pounds and the abnormal findings in the urine disappeared after intrauterine death and the patient remained asymptomatic until just before the onset of labor.

On Oct. 4, 1949, a few days after death of the fetus, blood studies of the coagulation mechanism were performed. The clotting time was 8 minutes. The clot which formed was normal in size and remained stable after incubation at 37° C. for 24 hours. The blood fibrinogen was 313 mg. per cent. A circulating fibrinolysin could not be demonstrated and tests for anticoagulants were negative. The platelet count was 323,000 and the prothrombin activity was 120 per cent.

During one of the routine visits to the outpatient clinic on Dec. 5, 1949, the patient stated that she felt well but volunteered the history of the recent appearance of "black and blue areas" of the skin in the absence of trauma. A tourniquet test was negative. Recently drawn venous blood formed a sliding gel in 10 minutes. Five minutes later the blood was completely fluid except for a barely visible fibrin clot. However, this tiny clot remained stable after 48 hours of incubation. The plasma fibrinogen concentration was 50 mg. per cent. Tests for fibrinolysin were negative. There appeared to be an increase in antifibrinolysin in the plasma but no anticoagulant activity could be demonstrated. Because of the critical reduction in fibrinogen, an accurate determination of prothrombin could not be performed until fibrinogen solution was added to the plasma sample. When this was done, the prothrombin activity was found to be 100 per cent. The platelet count was 200,000. It is believed that this is the first patient in whom a diagnosis of afibrinogenemia has been made prior to the onset of labor or bleeding.

In view of these changes in the coagulation mechanism, Mrs. R. was hospitalized on Dec. 5, 1949, although she was subjectively free of complaints. The liver function tests concerned in demonstrating parenchymal damage were normal except for a moderate elevation in the urobilinogen. The clotting studies were repeated on the patient and reaffirmed the presence of a fibrinogen deficiency. Thirty hours after hospital entrance, at 8:00 P.M. on December 6, the patient started to bleed vaginally. At this time it was noted that the vena puncture wounds made earlier in the day in securing blood samples had begun bleeding spontaneously. Although the venous blood sample clotted, the clot was extremely small and was again completely liquid within 15 minutes after formation. The blood fibrinogen was 35 mg. per cent and the prothrombin activity 60 per cent. Occasional uterine contractions became evident, accompanied by a moderate amount of vaginal blood which failed to clot.

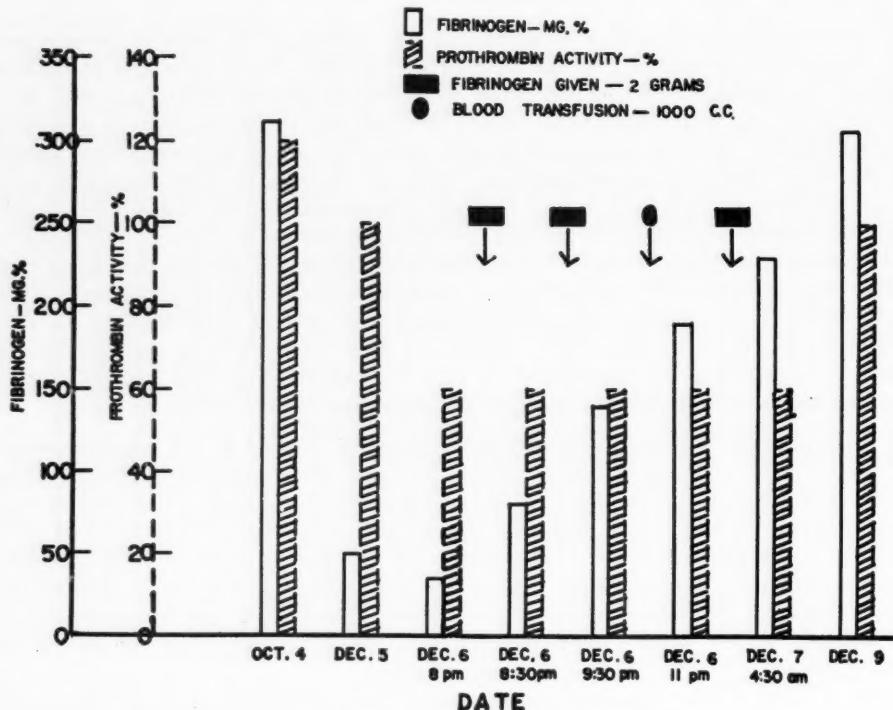


Fig. 1.—Blood changes in Mrs. R.

Replacement therapy with fibrinogen solution was instituted. It was decided that the amount of fibrinogen to be given would be based on the behavior of freshly drawn venous blood, i.e., clot formation and stability observed at frequent intervals.

At 8:30 P.M. 2,000 mg. of fibrinogen powder dissolved in 300 c.c. of 5 per cent glucose in water were given by intravenous infusion in an interval of 20 minutes. Ten minutes thereafter a small stable clot was evident in the clotting test, the blood fibrinogen was 80 mg. per cent and the prothrombin activity remained at 60 per cent. One hour after the first administration an additional 2,000 mg. of fibrinogen were given. Ten minutes later a much better clot was observed in the venous-blood clotting test, although the size of the blood clot was appreciably smaller than normal and an estimated half of the red cells remained free in the serum. Nevertheless, the needle puncture wounds on the arms were no longer oozing and small clots now appeared on the perineal pads. The fibrinogen concentration of the blood was 140 mg. per cent and a circulating fibrinolysin was not observed. The prothrombin activity remained at 60 per cent (Figs. 1 and 2).

About one hour after the second administration of fibrinogen the patient started in labor. In anticipation of further blood loss 500 c.c. of fresh blood and 500 c.c. of stored blood were given. The venous blood clot now appeared to be normal as to size, stability, and binding power effect on the red cells. Shortly thereafter, the fibrinogen concentration of the blood was 190 mg. per cent. The prothrombin activity remained at 60 per cent in spite of fresh blood transfusion.

The patient continued to labor during the next four hours, losing an estimated 400 to 500 c.c. of semiclotted blood by vagina during this time. At 4:00 A.M. on Dec. 7, 1949, the patient spontaneously delivered a macerated fetus in an intact ovisac. The placenta contained many old and fresh infarcts. The size and stability of the blood clot formed by the patient's blood at the time of delivery was satisfactory. However, immediately after delivery the bleeding appeared somewhat excessive in spite of a well-contracted uterus.

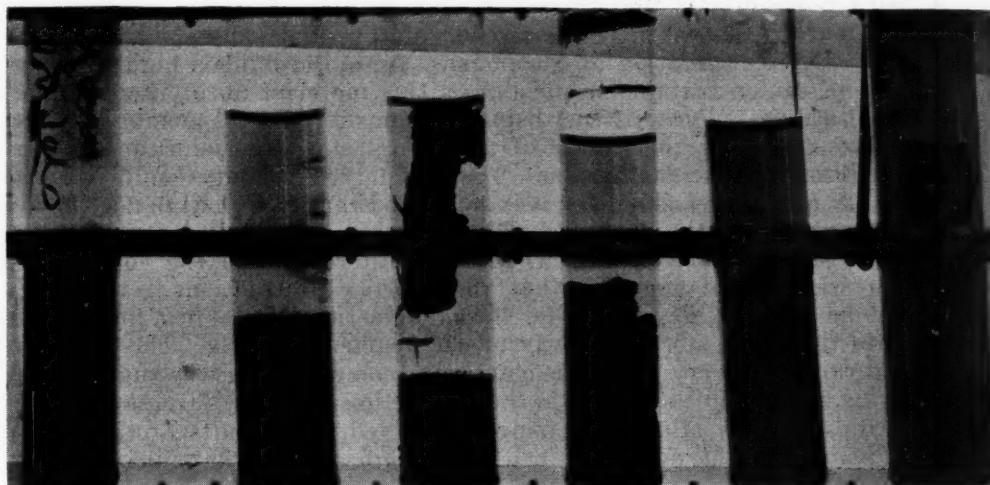


Fig. 2.—Blood clots in case of Mrs. R.

- Tube 1, December 6, 8 P.M., before therapy.
- Tube 2, December 6, 8:30 P.M., after 2 Gm. fibrinogen.
- Tube 3, December 6, 9:30 P.M., after 4 Gm. fibrinogen.
- Tube 4, December 6, 11 P.M., after 4 Gm. fibrinogen and 1,000 c.c. blood.
- Tube 5, December 7, 4 A.M., at delivery.
- Tube 6, December 7, 4:30 A.M., after 6 Gm. fibrinogen and 1,000 c.c. blood (one-half hour after delivery).

Therefore, an additional 2,000 mg. of fibrinogen were administered over a 5-minute interval and, thereafter, uterine bleeding ceased. One-half hour after the delivery the venous blood clot was normal, the fibrinogen concentration of the plasma was 230 mg. per cent and the prothrombin activity was 60 per cent. On the second postpartum day the fibrinogen concentration of the plasma was 306 mg. per cent, the prothrombin activity was 100 per cent, and venous blood formed a normal clot. Fig. 2 shows the changes in the values of fibrinogen and prothrombin during the acute phase of afibrinogenemia. The patient has been followed for three months and appears entirely well and the clotting mechanism has been normal at repeated examinations.

Comment

At present it is possible only to speculate as to the nature of the responsible etiological agent for the production of this transient afibrinogenemia. The products of pregnancy contained within the uterus would seem to bear a causal relationship to the fibrinogen reductions which have been described.

It is possible that some toxic placental or fetal substance depresses the production of fibrinogen by the liver. Only in the last patient in this series

was there an opportunity to study liver function prior to delivery. In this individual these studies were normal except for a moderate elevation in the urobilinogen.

Fibrinolytic digestion of plasma fibrinogen is another theoretical means by which the observed secondary afibrinogenemia could be produced.^{2, 3} In these instances during the acute phase of the disease when freshly drawn venous blood clotted, dissolution of the clot usually followed. However, it was impossible to demonstrate the presence of a circulating fibrinolysin by the destruction of standard fibrin clots by the patient's sera. Furthermore it has been demonstrated that when plasma fibrinogen is below a critical level, a clot may form that is unstable and cannot maintain itself.¹ In addition lytic factors are known to occur in the presence of shock.⁴

A third possibility is that thromboplastic material from the uterine contents gains entrance into the maternal circulation and causes intravascular coagulation with consumption of fibrinogen. Amniotic fluid is highly thromboplastic⁵ and under certain circumstances this material does enter the maternal blood stream. Perhaps the disintegration of the fetal membranes and placenta may allow for the escape of thromboplastic material from the placental site into the vascular system. The fibrinolytic activity could likewise be released in a similar fashion for it is suggested that this enzyme may be derived from necrosis of the decidua.⁶ The fact that these patients were about to enter or were in active labor when these alterations in the coagulation mechanism were noted suggests that the uterine contractions acting in a spongelike manner may express either thromboplastic material or a fibrinolytic enzyme into the blood stream by way of the venous sinusoids. The transient nature and rapid recovery from this condition soon after delivery suggest that labor may be a contributing factor in the production of this syndrome.

Regardless of the etiological factors involved, the results of this study would indicate that the syndrome can be recognized and that fibrinogen replacement therapy is the effective and simplest method of correcting the clotting defect. Obvious clot insufficiency evident by simple examination of venous blood allowed to clot is a quick method of detecting critical reductions in blood fibrinogen and indicates the presence of afibrinogenemia. Not only is the test necessary in the recognition of this syndrome but it will serve as an index in evaluating the effect of fibrinogen therapy. As a result of this easily performed test, this condition was recognized in the second and third patients at or before the onset of labor. The appearance of ecchymoses is a valuable sign and should suggest further examination of the blood.

The severe blood loss which these patients can experience when fibrinogen replacement is not given prior to or directly after delivery is believed amply demonstrated in the case of the first patient reported. Experience has shown that it is impossible to administer blood at a sufficient rate to increase the blood fibrinogen concentration to effective coagulant levels in these patients with afibrinogenemia who are bleeding actively.¹ Fibrinogen administration is the only method, short of complete replacement of the entire circulating blood volume, to produce normal coagulation and hemostasis in these desperate cases. For each pint of blood with a normal fibrinogen level of 250 mg. per cent is quickly diluted in the patient's circulation so that the effective fibrinogen increase would be only about 10 mg. per cent. In addition, it has been observed in patients with afibrinogenemia associated with severe premature separation, blood fibrinogen may be further consumed during labor. Therefore, it may be necessary to administer fibrinogen repeatedly to patients with afibrinogenemia through delivery and the first hour or two of the puerperium.

Experience is not sufficient to warrant a recommendation of the absolute amount of fibrinogen necessary to correct this hemorrhagic diathesis. There

was a marked diminution in vaginal blood loss in the first patient, following the infusion of 2,500 mg. of fibrinogen. However, in the light of present experience, it is believed an equal additional amount of fibrinogen might well have produced complete hemostasis and hysterectomy could have been avoided. The minimum effective dosage necessary to control postpartum hemorrhage is probably illustrated in the second patient. Three Gm. of fibrinogen decreased vaginal bleeding and re-established a stable clot in the test tube. The third patient who exhibited more severe symptoms required a total of 6 Gm. of fibrinogen finally to restore the clotting mechanism to normal. This would indicate that the total effective dosage must be equal to at least one-half of the total circulating fibrinogen.

Finally, emphasis must be placed on the dangers which are present in these cases should hysterectomy be seriously considered in the treatment of the hemorrhage. Their clinical behavior suggests that the usual methods of surgical hemostasis would not be adequate, unless the coagulation defect had first been corrected.

Conclusions

1. Afibrinogenemia may develop in an occasional sensitized Rh-negative patient carrying a dead fetus and unless this situation is recognized and promptly treated, serious hemorrhage may occur at the time of labor and delivery.
2. The diagnosis of secondary afibrinogenemia can be made while the patient is asymptomatic and prior to the onset of labor.
3. The absence of a clot or a marked decrease in the size and stability of the clot formed by a few cubic centimeters of freshly drawn venous blood will detect a critical reduction in blood fibrinogen concentration.
4. Fibrinogen replacement restores coagulability of the blood in the test tube and in the patient. Six thousand mg. of fibrinogen appears to be the correct total amount to administer.
5. It is likely that, should the hemorrhage be due to afibrinogenemia alone, hemostasis will follow fibrinogen replacement and further treatment will be unnecessary.
6. Hysterectomy for the control of postpartum hemorrhage must be avoided in the afibrinogenemia patient until the coagulation mechanism has been restored.

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221 LONGWOOD AVENUE.

Discussion

DR. JOHN L. MCKELVEY, Minneapolis, Minn.—Information is rapidly accruing in the various aspects of the physiology, biochemistry, and pathology of blood. That portion of the field which deals with blood coagulation has begun to yield to careful study. While the classical explanation propounded by Morowitz early in this century still forms the basis of present-day concepts, it is now evident that the whole problem is much more complicated than it at first appeared and probably even more than is now suspected. Real contributions to an eventual understanding of the mechanisms involved are being made by

numerous groups of workers here and abroad. Among our own group, Dieckmann, Smith, and Reid's group at the Boston Lying-in and the Thorndike Laboratory have pointed up the obstetric aspects. That this has a practical significance must be evident to all who have given attention to their reports.

It must now be recognized that there is a definite pathologic process which leads on to interference with blood coagulation mechanisms and so to severe bleeding. There is interference with the prothrombin-thrombin series and with the fibrinogen-fibrin series as well. These seem to be separate since the artificial correction of one does not correct the other. There is strong evidence that the interference with fibrinogen and fibrin is due to so-called fibrinolysis. Increases in prothrombin time seem to run parallel with this but whether or not it is due to the same cause is still to be proved. Fortunately, a rapid and reasonably satisfactory gross test is available.

Dr. Reid has mentioned the circumstances which are known to give rise to this condition. In general, as it occurs in the human being, they are disease states with the common factor of peripheral vascular collapse and shock. Now Dr. Reid presents us with a demonstration that it can also occur under other circumstances. One would not have expected it to occur with intrauterine fetal death in the absence of placental separation. Can Dr. Reid assure us that there was no evidence of premature separation of the placenta in the patients whose findings he presented? It is evident that the condition preceded shock.

There are many features of the condition which require study. It is evident that the naturally occurring and the experimentally produced conditions which lead on to depletion of fibrinogen, prolongation of prothrombin time, and to at least the frequently demonstrable presence of a fibrinolysin, will produce that state in only a small proportion of the individuals so affected. There is a missing link here. Has Dr. Reid any suggestion as to what it is?

This work also lends support to the opposition to the use of blood substitutes in the treatment of the various types of shock. Indeed, it is clear that citrated stored blood given by present-day techniques is itself in many ways not whole blood but a sort of blood substitute. Would Dr. Reid care to add to what he has already said regarding the use of stored blood in this condition?

Some further details as to the preparation, stability, and administration of fibrinogen would be appreciated.

There is no doubt but that this report will stimulate interest among obstetricians and gynecologists in the recognition and study of the condition. It is already a significant clinical contribution.

DR. REID (Closing).—The methods used in this study were directed toward investigating the known factors in blood clotting. We have consoled ourselves in our lack of understanding of all of the features of the coagulation mechanism by the realization that there is considerable disagreement between authorities in this field. Furthermore, certain of the methods used in studies concerned with the clotting mechanism are not completely standardized which explains some of the variations in results.

With respect to banked blood, the fibrinogen content remains stable but there is some evidence that the prothrombin activity may become decreased. Hence, one should consider the administration of freshly drawn blood to these patients. Fibrinogen is now available for clinical use under the Red Cross Blood Program.

Regarding the fibrinolytic activity, a review of the literature of patients who die of amniotic fluid embolism reveals that those who survive the original shock succumb from an associated postpartum hemorrhage. This poses the question as to whether the blood in such cases becomes defibrinated by the thromboplastic content of the amniotic fluid. In addition, this points up the process as to whether these noxious substances within the amniotic fluid may not irritate the lungs to release a large amount of fibrinolytic enzyme. This is in line with Tagnon's observations that in conditions of shock it was noted that the parenchymal tissue of the lung was a rich source of this enzyme.

THE MANAGEMENT OF THE PREGNANT DIABETIC WOMAN AND HER NEWBORN INFANT*

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HERE is much confusion concerning the problems and the management of the pregnant diabetic patient and her child. From a survey of the literature, it is evident that there is some general agreement that diabetic mellitus is associated with a lowered fertility rate and an increased loss of fetal life. This increase is due to abortion, death in utero, and intrapartum death, and extends into the neonatal period.¹⁻⁶ However, from the analyses reported to date, it is impossible to state with any degree of assurance that these are related directly to the disordered physiology of the diabetic individual. In addition, the published studies differ quantitatively from each other. For example, the incidence of toxemia varies from over 50 per cent^{6, 8} to the rate usually found in the nondiabetic woman (7 to 8 per cent). Attempts have been made in recent years to blame disturbances in hormone levels for the development of toxemia of pregnancy.^{9, 10} Increased abortion rates, the higher fetal mortality rates, and a marked increase in the frequency of toxemic states in pregnant diabetics^{6, 9} have been ascribed to high serum chorionic gonadotrophin and low steroids with a constant and marked fall in serum estrogen and a lowered excretion of sodium pregnadiol glycuronate.

It has been observed for many years that the weight of babies born to diabetic mothers is abnormally high.^{3, 6} This is due in part to rapid growth, and in part to water imbibition. Recently, evidence has been presented to show that the birth weight of children of prediabetic mothers was also abnormally increased.¹¹ There has, as yet, been no adequate explanation of this observation.

The reason that the literature on experimental diabetes does not illuminate these problems at all is due to two factors. The first is that this problem has not been adequately studied in a suitable animal; the second is that no form of experimental diabetes is an exact replica, etiologically or otherwise, of diabetes mellitus in the human being.

Diabetes mellitus is a syndrome characterized by persistent hyperglycemia and secondary glucosuria. The severity of the disturbance varies from individual to individual and from one period of the individual's life to another. In many individuals there is definite evidence of a genetic predisposition. In others, it is preceded by an obesity of many years' standing. In a small minor-

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ity of instances the causative factors become evident because of associated findings pointing to a disturbance in function of one of the endocrine glands or of the liver. Thus, there is a diabetes associated with acromegaly, Cushing's disease, hyperthyroidism, pheochromocytoma, and hepatitis. The vast majority of patients, however, present no such etiological clues. Their cases are, in all probability, due either to absolute insulin deficiency or to the relative preponderance of one of the numerous factors antagonistic to insulin action. It becomes obvious, therefore, that diabetics may react variably to the physiological load of pregnancy, depending upon the basic etiological factor or factors which may have caused the diabetic state. It may be that pure insulin-deficiency diabetes will produce a different reaction in the placenta and the fetus than will the diabetes caused by a relative preponderance of adrenal cortical steroids or one caused by hepatic dysfunction. The time has come when attempts should be made to differentiate diabetes into etiologically uniform groups and to study the behavior of each group separately.

Another important factor which could play a role in the degree of variance of behavior in pregnant diabetics may lie in the general nutritional status of these individuals before and during pregnancy. The criteria used by various centers for the adequate control of diabetes differ. Some pay particular attention to the general health, freedom from all symptoms, etc., but allow moderate to high glycosuria. Others focus their primary attention on adjusting the hyperglycemia and glycosuria to as nearly normal as possible. It may be that the placental tissue of diabetics of long standing may require somewhat higher blood sugars than that of metabolically normal women and that "strict" control is not always best for a particular condition or organ. Adequacy of protein intake is another pertinent question since complications of pregnancy in the nondiabetic population are said to be more frequent when the protein intake is below normal.

Finally, it has been shown that the known duration of the diabetic state is of great importance in the development and degree of vascular complications of diabetes.¹² Degenerative vascular changes in the maternal portion of the placenta of the diabetic might be expected to appear earlier than in the placenta of the normal patient. If such changes do occur, more frequent complications should be found in pregnant diabetics and particularly in those whose diabetes is of long standing.

Placentas of Diabetic Women

In order to find an answer to this question, ten placentas obtained from diabetic women were studied. Multiple blocks were cut from the placentas which had been fixed in formaldehyde. Paraffin sections were made and the following stains used: hematoxylin and eosin, iron hematoxylin and eosin, Giemsa, and van Gieson stains.

No consistent changes were found. Varying degrees of infarction were found in four placentas. Calcification was found in five instances. In some placentas the giant cells were more hyperchromatically stained than normal. This was particularly pronounced in three instances. Degenerative changes of villi with some edema were present in three instances. There was no excessive connective tissue present in any placenta.

Though certain changes were found in the placentas, they do not vary either quantitatively or qualitatively from those seen in patients without diabetes.

Prediabetic Pregnancies

This study is an analysis of 163 pregnancies of 52 diabetic patients who were delivered at Michael Reese Hospital during the past 15 years. Sixty-nine pregnancies occurred during the prediabetic period in 17 women. Fifty-six were carried to viability and 13 ended before viability. These latter have been eliminated from further discussion because (1) it was impossible to determine how many abortions were spontaneous and how many might have been induced, (2) the abortion rate (18.8 per cent) approximates that found in the non-diabetic, and (3) it is believed that statistics based upon the accuracy of the patient's memory are of little or no value.

These 56 viable pregnancies occurring in the prediabetic years resulted in 52 living children (93.0 per cent) whose birth weights ranged from 2,494 grams to 5,443 grams—the average being 3,638 grams. There were 2 stillborn infants and 2 neonatal deaths. These 4 infants averaged 5,670 grams in weight. Sixty-three per cent of the recorded birth weights were above the normal average of 3,400 grams. The average birth weight of the entire group of 56 babies was 3,939 grams. The excessive weight of the 2 stillborn infants and of the 2 infants who died during the neonatal period placed these 4 infants among the largest 6 infants of the entire series. These deaths might well be attributed to the obstetric mishaps which so frequently accompany fetal oversize although this is difficult to ascertain from the records.

This somewhat increased incidence of large babies, stillbirths (3.5 per cent), and neonatal deaths (3.5 per cent) is in agreement with Paton,¹¹ who also found such increased rates in an analysis (by history only) of 122 diabetic women who had had 454 pregnancies during their prediabetic years, and with Herzstein and Dolger,¹³ Allen,¹⁴ Gasper,¹⁵ Cameron,¹⁶ and Palmer and Barnes,¹⁷ who found a definite increase in both the stillbirth and the neonatal death rates in pregnancies which occurred during the five years immediately preceding the onset of the diabetes.

On the other hand, this increase in fetal loss in no way approximates that reported by Gilbert and Dunlop¹⁸ who found a prediabetic fetal loss three times that of a control series if the diabetes appeared before the age of 45 years and six times as great in those pregnancies which occurred in the two years immediately preceding the onset of the diabetes. In our series, all patients were under 45 years of age, the diabetes either was present or occurred during the childbearing years, and it so happened that none of the fetal deaths occurred in the two years immediately preceding the discovery of the diabetes. It is unfortunate that compiled statistics frequently include abortion loss as part of fetal loss. As previously mentioned, abortion rates seem inaccurate at best and particularly so when statistics are based on interviews with older diabetic women. Under such circumstances all statistics must be based on memory over many years—memory which at best must be vague and hazy.

Pregnancies in Diabetic Patients Delivered Elsewhere

Fourteen of the patients in this series had 22 pregnancies after the onset of the diabetes but before coming under our care. There were 4 previable and 18 viable pregnancies. Thirteen of the viable babies survived (72.2 per cent) and 5 were lost. The birth weight of the stillborn babies was said to be over 3,800 grams and it would seem that these 5 might have been salvaged if proper attention had been paid to intrauterine size and maturity. In addition, there

were 2 full-term living babies who could not be classified because it was impossible to determine whether they were born before or after the onset of the diabetes.

Clinical Course and Results in Diabetic Pregnancies Under Our Care

Fifty-two diabetic women had 70 pregnancies after the onset of the diabetes and while under our care. Eleven (15.7 per cent) ended before viability and 59 were carried beyond viability. Fifty-three of the 59 pregnancies resulted in live births (89.8 per cent). Fifty-one of these 59 babies were well when they left the hospital. There were 2 neonatal deaths. One baby weighed 2,520 grams (32 weeks) and was delivered as a breech following premature separation of the placenta. The baby lived a few hours. There was no evidence of toxemia in the mother. The second neonatal death occurred in a full-term baby delivered by cesarean section. This baby was cyanotic at birth and died in a few hours. The mother was a mild diabetic who lost 17 pounds during pregnancy in spite of a hydramnios. At the time of cesarean section, her blood pressure was 164/112 and there was one plus albumin. There were no edema and no casts in the urine. The cause of this death was not ascertained.

Four viable fetuses died in utero before the onset of labor while 2 were lost during delivery. Of the latter, one was a 2,100-gram fetus with congenital anomalies; the other weighed 5,216 grams and died during delivery as a result of shoulder impaction. All stillborn babies were delivered vaginally. Thus the over-all fetal salvage of viable babies was 86.4 per cent.

There is a considerable variation in the reported frequency of fetal abnormalities and fetal presentation. It has been stated that the fetus of a diabetic woman stands one chance in six of having gross abnormalities, and that one out of every three will be a breech presentation. In this series there were only 7 breech presentations (11.1 per cent). Of these, 1 was delivered at 32 weeks, 1 at 34 weeks, 2 at 36 weeks, and 3 at 38 weeks. This is in accord with the usual increased incidence of breech presentation in patients prior to term.

Hydramnios was observed in 6 pregnancies (9.5 per cent) and there were no associated congenital anomalies. Only one baby in the entire series showed a major congenital defect. This was the 2,100-gram fetus who died during labor; autopsy revealed a patent intraventricular septum. One other baby had a slight degree of hypospadias.

Mode Of Delivery

Only 10 pregnancies were allowed to go to term. Four of these ended in cesarean section and 6 in vaginal delivery. Two of the latter resulted in the babies who died during delivery.

There were 26 vaginal deliveries (44.0 per cent) which resulted in 20 live births. The average weight of these babies was 3,847 grams (2,600 to 4,840). Only 4 of these living babies were delivered at term. Six vaginal deliveries ended with fetal loss.

TABLE I. VAGINAL DELIVERIES

	WEEKS OF PREGNANCY										
	30	32	33	34	36	37	38	39	40	?	
Stillborn		1	1	1	3	2	3	3	4	2	
Living		1	1				2		2		

Analysis of the 6 vaginal deliveries leads to the inescapable conclusion that 3 babies might have been saved if proper attention had been paid to fetal size and maturity. One baby weighing 5,556 grams and one weighing 4,810

grams died in utero during the thirty-eighth week of pregnancy. The third baby, weighing 5,216 grams, died during delivery because of the delay due to impacted shoulders. The fourth baby was not salvageable because of congenital anomalies. Thus 3 of the 6 viable babies that were lost might have been saved.

There were 33 babies delivered alive by cesarean section. Seven were delivered in the thirty-sixth week, 8 in the thirty-seventh week, 7 in the thirty-eighth week, 5 in the thirty-ninth week, and 4 after the thirty-ninth week. In 2 instances the duration of gestation was not recorded.

TABLE II. DELIVERY BY CESAREAN SECTION

	WEEK				
	36	37	38	39	40+
Number*	7	8	7	5	4
Average weight in grams	3,603	3,558	3,514	3,426	3,454

*In 2 the gestation was not recorded.

The average birth weight of all babies delivered by cesarean section was 3,525 grams. This is 327 grams less than the average of those babies who were allowed to deliver vaginally. It is also of interest to note that the average weight of the babies delivered in each week group is practically the same. It is apparent that these pregnancies were terminated when it was felt that further intrauterine existence might endanger fetal life. However, it must be recognized that there is no rule of thumb for estimating intrauterine maturity or intrauterine weight.

The decision for the time of termination of pregnancy is arrived at by a consideration of the obstetric history and the estimation of fetal size by abdominal palpation and x-ray. The latter is of value not only for the diagnosis of size, position, and presentation, but also in ascertaining the presence of gross fetal anomalies and multiple pregnancy.

The decision for the method of delivery is a simple obstetrical problem. The primigravida with her long closed cervix is best delivered by cesarean section. The multigravida with a soft and dilated or dilatable cervix is best delivered vaginally after labor is induced by simple rupture of the membranes and drainage of the liquor amnii. The multigravida with an excessively large baby or a long closed cervix is best delivered by cesarean section.

It is impossible to compare the results of vaginal delivery with those of cesarean section. The reason for this lies in the fact that all of the known fetuses dead in utero were allowed to deliver vaginally. The record of each fetal death in utero was studied. Only in 4 instances was it possible to ascribe a reasonable cause. As previously mentioned, 1 fetus was born at term with fetal anomalies, 1 was lost during delivery (5,216 grams), while the other 2 (5,556 and 4,810 grams) died in utero at the thirty-eighth week. There was no evidence of toxemia in any of these mothers. The fetuses apparently died of "diabetic postmaturity," a phrase which we believe to be descriptive of the fetus of a diabetic mother which has been permitted to remain in utero too long. Such a fetus may not be postmature chronologically, but it has become excessively large for reasons not completely understood. Such excessive size frequently is associated with sudden death in utero as term approaches or marked dystocia from excessive bulk. The remaining 2 fetal deaths in utero occurred between the thirtieth and thirty-fourth week. In none of these was there an apparent or demonstrable cause for fetal death. The total fetal salvage of the entire group of pregnancies carried beyond viability was 51 out of 59, a fetal survival rate of 86.4 per cent.

TABLE III. ONE HUNDRED SIXTY-THREE PREGNANCIES IN 52 DIABETIC PATIENTS

	NO.	TOTAL NO. PREG- NANCIES	PRE- VIABLE	VIABLE	STILL- BORN	NEO- NATAL DEATHS	LIVING
Prediabetic	17	69	13	56	2	2	52
Diabetic elsewhere	14	22	4	18	5		13
Diabetic Michael Reese Hospital	52	70	11	59	6	2	51

Toxemia of Pregnancy in the Diabetic

There has been considerable discussion in the recent literature concerning the frequency of toxemia in the diabetic pregnant patient. The theory has been advanced that toxemia of pregnancy is primarily due to a hormonal imbalance.⁹ It has been further postulated^{5, 6} that this imbalance occurs more frequently in the pregnant diabetic and that therefore toxemia of pregnancy is markedly increased in these patients. This has not been our experience. There were only 6 patients who developed evidence of mild to moderate pre-eclamptic toxemia. In each the systolic blood pressure rose to levels of 150 to 178, the diastolic to 90 or more, and the amount of albumin varied from one plus to four plus. Two of these 6 patients had moderate edema. All 6 responded to the usual conservative management of pre-eclamptic toxemia, none presented any major problem. Five of the 6 babies survived; one was cyanotic at birth (cesarean) and died within a few hours. Of the 59 pregnancies in this series one was complicated by pyelonephritis, without hypertension or edema. There were 2 hypertensive patients whose hypertension existed prior to pregnancy and was not aggravated by the pregnancy. Neither of these patients developed albumin or edema.

This incidence of toxemia, 6 in 59 pregnancies (10.2 per cent), is almost as low as our incidence in nondiabetic patients (7 to 8 per cent). It is, therefore, difficult to accept diabetes as a predisposing or direct cause of toxemia of pregnancy. Perhaps it is worth repeating that the only instance of premature separation of the placenta occurred in a patient who did not have any of the stigmas of toxemia.

Management of Diabetes and Pregnancy

Evaluation of Factors Before Pregnancy.—

The uncontrolled diabetic of today is no different from the diabetic of the preinsulin era. She frequently presents the problem of infertility but should she achieve a pregnancy she faces the real risk of losing both her life and that of her baby. The advent of insulin has increased the fertility of the diabetic woman, has made her chances of survival similar to that of the nondiabetic, and has increased tremendously the fetal salvage.

On the other hand, this same advent of insulin has given rise to a new problem. The juvenile diabetic who has been helped to survive, mature, marry, and reproduce faces the problem of premature vascular sclerotic changes. The possibility of these changes must be evaluated before pregnancy is permitted. This premature vascular aging of the diabetic is well known. These manifestations include x-ray evidence of calcification of the iliac vessels, retinopathies, coronary heart disease, and nephritis which has usually proved to be intracapillary glomerulosclerosis. White⁶ found them in 70 per cent of her patients whose diabetes had had its onset in childhood and who had survived twenty years of the disease. Dolger found eye changes, i.e., retinopathies, in 100 per cent of his subjects. Evidence of any or all of these forms of blood-

vessel degeneration should be sufficient for the interdiction of pregnancy, for it is a well established fact that any woman with renal and blood-vessel damage runs a very grave risk in assuming the added metabolic load of pregnancy. The arteriosclerotic and nephritis are never good obstetric risks, and many of these will show hypertension, albuminuria, and edema only during the latter months of pregnancy. It would, therefore, seem rational to assume that a preponderance of diabetic patients with sclerosis would then show a high incidence of hypertension, albuminuria, and edema.

Careful evaluation of these factors is necessary to determine whether a patient can or cannot safely carry a pregnancy without the risk of renal breakdown. This type of evaluation may be one of the reasons for the low incidence of toxemia presented in this report. A second factor may be found by studying the duration of the diabetes. Twenty of our patients had diabetes for one year or less, 24 had diabetes for one to five years and 11 for six to ten years. Only 9, one out of every six patients, had diabetes for more than ten years. Thus diabetes of long standing was relatively uncommon in our patients.

TABLE IV. DURATION OF DIABETES

No. patients	YEARS			
	1 YEAR OR LESS	1-5	6-10	11 OR MORE
	20	24	11	9

The patient's age at the onset may likewise be a factor. In this series, the age of onset was under 20 years in only 15 (33 per cent) and over 20 years in 30 patients (67 per cent). This relatively low incidence of juvenile diabetes with its concomitant low incidence of long-standing diabetes may play a definite role in the low incidence of toxemia.

TABLE V. AGE AT ONSET OF DIABETES

No. patients	AGE IN YEARS			
	UNDER 10	11-20	21-30	31-40
	1	14	18	12

Evaluation of Factors During Pregnancy.—

Diet: The amount of total calories prescribed for the patient is dependent on the nutritional state of the mother. Those who are obese should be given approximately 20 calories per kilogram based on the ideal weight in order to reduce their weight. Those who are underweight should be given approximately 35 to 40 calories per kilogram in order to increase their weight. Those who are normal in weight are usually given 25 to 30 calories per kilogram. The diet should be liberal in carbohydrate with a minimum of 200 Gm. daily, except in the occasional patient who is markedly overweight to whom less should be given. Protein is usually given in amounts of 2 Gm. per kilogram. Fat is given in the amount that is necessary to complete the caloric prescription. Throughout the construction of the diet, the tastes and appetite of the patient should be consulted. Modification must be made for those conditions inherent to pregnancy which have a tendency to upset the normal prescribed intake of food.

Insulin: There are many diabetics who are well regulated without insulin and who do not require insulin at any time during the pregnancy. There are others who are well regulated without insulin when not pregnant but who require insulin during pregnancy. The diabetic woman on insulin therapy may, when she becomes pregnant, (1) remain on approximately the same dosage

throughout, or (2) may require more insulin, or (3) may require less insulin, especially in the latter part of the third trimester. No satisfactory explanation is at hand for this variation. Most patients can be regulated satisfactorily with the use of protamine zinc insulin given once daily, although some require a mixture of regular insulin and protamine zinc insulin given as a combined dose before the morning meal. However, there are some who are more refractory and who require a dose of regular insulin before each meal. These latter patients can be adequately managed only by examination of pre-meal urine specimens and the insulin dosage regulated according to the amount of sugar and acetone found in each specimen.

The amount of insulin used in all of these categories should be sufficient to keep the patient in metabolic balance. This means the avoidance of acetonuria, the maintenance of the blood sugar at a lower level, a reduction of the glycosuria, and above all the development and maintenance of *a sense of well-being*. This latter can be accomplished best by permitting a slight amount of glycosuria, i.e., up to 15 grams per 24 hours, thus avoiding the risk of recurrent episodes of hypoglycemia. Therefore, no emphasis should be placed on the maintenance of a sugar-free urine.

The amount of insulin necessary varies with each individual patient, and may vary from time to time throughout the pregnancy. Adequate dosage to accomplish these aims can be judged only by the results achieved. There is no other yardstick for the dosage of insulin required.

The renal threshold: The ability of the renal tubules to resorb glucose from the glomerular filtrate is often altered in the pregnant diabetic. Thus there may be marked glycosuria present without the concomitant hyperglycemia. If the factor of the altered renal threshold is not kept in mind, and regulation of the diabetic state is attempted by the guidance of the urinary sugar alone, overdosage with insulin may occur. The failure to supply an adequate intake of carbohydrate to compensate for the loss of glucose through the altered renal tubules can lead to ketosis. To prevent these complications, one needs to be guided by the blood sugars, by the weight gain, and by frequent and repeated determinations of glycosuria and acetonuria.

Hyperemesis gravidarum: The frequent nausea and vomiting which occur in the first trimester of pregnancy always result in a disturbance of sugar balance in the diabetic. It is difficult under these conditions to control the hyperglycemia and glycosuria and to maintain normal body weight and prevent acidosis.

Hyperemesis gravidarum in all but the most severe forms is best controlled by small frequent feedings and mild sedation. It is advisable, therefore, when this occurs in the pregnant diabetic woman, to eliminate a depot of long-acting insulin. Temporarily regular insulin should replace protamine zinc insulin. It should be given in small divided doses, which dosage is gauged by the determination of sugar and acetone in the pre-meal urine specimens. When the hyperemesis gravidarum is severe enough to preclude oral feedings and to demand feeding by parenteral fluids then regular insulin should be administered. This insulin should be given partially by the subcutaneous route and partially intravenously with the parenteral fluids. The dosage must be gauged by the amount of sugar and acetone found in the urine. Tests for these latter substances should be made at frequent intervals.

Management of Diabetes During Toxemia of Pregnancy

Pre-eclamptic toxemia can and does occur in the diabetic pregnant woman. In the series here reported, the incidence of pre-eclamptic toxemia in the dia-

betic group did not exceed greatly the generally accepted incidence for the non-diabetic pregnant patients (7 to 8 per cent). As previously mentioned, it would seem that long-standing diabetes, with its resulting premature vascular aging may be a causative factor in the production of a toxemia-like picture. When the diabetic pregnant woman, with an altered hepatic physiology, i.e., low glycogen reserve, and/or a fatty infiltration of the liver from inadequate metabolic management, develops a superimposed toxemia of pregnancy, special problems of management arise.

In addition to an attempted restoration of electrolyte and water balance and the administration of the usual glucose to prevent hepatic failure, a switch must be made immediately from long-acting insulin to the shorter-acting insulin. The careful use of regular insulin in the presence of liver damage is necessary, since increasing liver failure can result in a liver that is hypersensitive to the insulin and a rapid hypoglycemia may develop. Such a hypoglycemia may be fatal or may result in cerebral damage. Evaluation of the blood-sugar level at frequent intervals is important. More important, however, is constant vigilance with respect to the appearance of ketone bodies in the urine. The appearance of acetone and diacetic acid in the urine in the presence of an increasing glycosuria is evidence of inadequate insulin therapy. The appearance of acetone and diacetic acid in the urine in the presence of decreasing or absent glycosuria is evidence of inadequate administration of carbohydrate or of too much insulin or, last, of evidence of a liver that is irreversibly damaged.

Under all of these conditions the amount of insulin and the frequency of its administration can be determined only by the demonstrable effect of each individual dose upon the total clinical picture.

Hormone Therapy

In 1934 Smith and Smith²⁰ reported that hormone metabolite concentrations in the urine and blood of toxemic patients differed from those found in normal pregnancy. In 1938 Browne, Henry, and Venning reported a lowered excretion of pregnandiol associated with toxemic pregnancy. White⁶ reported an imbalance of sex hormones in 75 per cent of 300 diabetic pregnancies. This imbalance consisted in the fall of the serum estrin level, and a decreased secretion of sodium pregnandiol glycuronate. She also reported a rise in the chorionic gonadotrophic level which was felt to be a compensatory mechanism. To these disturbances in the sex hormone production and levels are attributed (1) a high incidence of toxemia, and (2) a markedly increased fetal loss. Hypoovarianism is cited as the probable primary problem and it is stated that the placenta attempts to compensate for early ovarian deficiency by rapid maturation which in turn is followed by just as rapid and somewhat premature aging of the placenta.

There was no clinical evidence of hypoovarianism in this group of 52 diabetic patients. The menstrual history of all patients was within the range of normal. There were no instances of prolonged amenorrhea nor of sterility. The total fertility rate up to the time of this analysis was 3.1 pregnancies per patient and the fertility rate after the discovery of diabetes was 1.8. These rates give no indication of decreased fertility in either the prediabetic or diabetic years. Undoubtedly some of these women will have additional pregnancies which will further increase the fertility rate during the diabetic years.

The administration of diethylstilbestrol in increasing daily doses is presumed to stimulate progesterone secretion thus restoring the normal hormonal balance and preventing immature and premature labor and toxemia of pregnancy. Recently Smith and Smith²¹ have shown that the administration of diethylstilbestrol to normal nondiabetic women resulted in larger, longer,

heavier, and more mature babies with a definite decrease in the incidence of prematurity.

Sommers, Lawley, and Hertig²² investigated the effects of this same diethylstilbestrol therapy upon the weights of baby and placenta in the same group of women. They state that "weights of both baby and placenta are increased in stilbestrol-treated full-term and premature births"; and that "stilbestrol stimulates increase in weight and presumably size of both infant and placenta." They further found a more frequent occurrence of marked placental calcification and intervillous thrombosis in full-term stilbestrol-treated placentas and a definite incidence of mature chorionic villi and intervillous thrombi in the placentas of stilbestrol-treated patients who delivered prematurely.

It is difficult to reconcile these reports. On the one hand, increasing and continuing administration of diethylstilbestrol is used because it prevents immature and premature delivery, because it lowers toxemia, and finally because it is said to increase fetal salvage. Yet, in White's report, labor was terminated early in the vast majority of instances, by cesarean section in the thirty-sixth to the thirty-seventh week, to prevent fetal overmaturation and placental overmaturation with their accompanying obstetrical problems of oversize and overweight fetus and of fetal death in utero. On the other hand, the same increasing and continuing administration of stilbestrol is observed by Smith and Smith to result in longer, larger, heavier and more mature babies and that "significantly more babies of stilbestrol-treated mothers weighed over 8 pounds and were more than 21 inches long at birth."

These latter observations would seem therefore to contraindicate the use of diethylstilbestrol in the diabetic pregnant woman, since it is a well-established fact that a considerable proportion of the increased fetal loss in diabetic pregnancies is due to the dystocia which results from fetal oversize.

Furthermore, diethylstilbestrol therapy would seem contraindicated in the diabetic pregnant woman to avoid rapid or early placental senescence and to prevent some of the inexplicable fetal deaths in utero which are known to occur in the latter weeks of pregnancy.

Further confusion concerning this entire problem results from reports by Rubin, Dorfman, and Miller,²³ who found high serum chorionic gonadotrophin levels in a patient with normal serum estrin and normal pregnandiol excretion, and the recent report of Davis and Fugo,²⁴ who could find no evidence that diethylstilbestrol stimulates the production of steroids by the corpus luteum or the syncytium.

It would seem, therefore, unnecessary to subject pregnant diabetic women to the routine of continuing and increasing doses of diethylstilbestrol and progesterone until such a time as this problem has been clarified and the conflicting reports reconciled.

No sex hormone therapy was used in any of the patients in the series here reported.

Predelivery, Delivery, and Postdelivery Management

At least three, and preferably seven days before the expected termination of pregnancy, the insulin used should be changed from protamine zinc insulin or the mixture of regular and protamine zinc insulin to regular insulin. This should be given in divided doses before each meal, thus avoiding the action resulting from a depot of long-acting insulin at a time when the food intake must of necessity be variable. Hypoglycemia may be avoided more readily in this way. This regime continues until the termination of the pregnancy, either by induction of labor or by cesarean section.

Oral feeding is contraindicated immediately prior to cesarean or induction of labor and should not be resumed until the patient has recovered from either procedure. During this period dehydration and ketosis must be avoided. This can be done best by the use of intravenous glucose solution and saline with sufficient regular insulin to prevent marked hyperglycemia and ketosis. No attempt should be made to maintain a completely sugar-free urine since there are no harmful effects resulting from a mild but continuing glycosuria. The increased muscle effort which accompanies labor and vaginal delivery may deplete the glycogen reserve in the liver. This may further upset the sugar balance and make control more difficult.

Best results are obtained usually by the administration of 2,000 c.c. of 5 per cent glucose in normal saline and 1,000 to 2,000 c.c. of 5 per cent glucose in water for twenty-four hours. This limits the salt intake to 18 Gm. per day. Such a salt intake is contraindicated when toxemia of pregnancy or cardiovascular renal disease is present. On the other hand, excessive vomiting or hemorrhage demands an increased salt intake.

When oral feedings are resumed regular insulin should be given before each meal until the glycosuria has once again become stabilized. Then the long-acting insulins may replace the regular insulin.

The Newborn Infant

The effect of the maternal diabetes and of its treatment upon the newborn infant was studied. In order to establish our own basis for comparison, serial blood-sugar determinations were made at frequent intervals on 19 normal mothers and their newborn infants. "True blood-sugar" values were obtained by the Somogyi modification of the Shaffer-Hartman micro-method (adult normal range 70 to 95 mg. per cent). It was found that the blood-sugar level of normal newborn infants during the first twenty-four hours of life, and particularly during the first hour, is so unstable as to limit the significance of any single isolated determination. The average of all infants' blood-sugar values obtained at birth was 57 mg. per cent. There is a tendency for higher values to fall, and for lower values to rise within the next four hours. The average value at the end of this period is 45 mg. per cent. Although 3 infants during the first four hours of life, exhibited symptoms which were possibly associated with hypoglycemia, 4 other infants showed as low or lower levels without symptoms. Thus, in confirmation of the work of others,⁵ the blood-sugar level in itself is not a good indication of "clinical hypoglycemia" in newborn infants. With the onset of feeding at the end of the first twenty-four hours, a slow but steady rise in blood sugar occurs. By the tenth day of life the average value for all infants is 67 mg. per cent. It is apparent that the adult normal range of blood-sugar level does not apply to newborn infants.

Serial blood-sugar determinations were made at frequent intervals on 20 babies of diabetic mothers. The same method of chemical determination was used. The blood samples were drawn at frequent intervals during the first hour of life and thereafter at hourly intervals or longer. In comparing these values with those of "normal" newborn infants it was found that the blood sugar of babies born of diabetic mothers falls more rapidly during the first hour of life, falls lower, and returns to normal more slowly.

An unusual example of this rapid fall in the newborn blood-sugar value has been added to Fig. 2. This patient was seen in consultation in another institution just prior to cesarean section. She was poorly regulated and was in severe acidosis. Her blood sugar was 380 mg. per cent, cord blood sugar was 360 mg. per cent, and blood drawn from the

infant was 148 mg. per cent at 30 minutes and 26 mg. per cent in one hour. These extremely high values are completely at variance with those found in well-regulated diabetic mothers and their newborn infants and the rapid and marked fall in the baby's blood-sugar level was dramatic. It is believed that the explanation of this rapid fall in blood sugar lies in the failure of the newborn liver to release glucose rapidly.

The Newborn Infant of the Diabetic Mother

The characteristic of the newborn of the diabetic mother is this marked fall in blood sugar that occurs within the first hour after birth. This rapidly developing hypoglycemia is not attended by any clinical evidence of the dangerously low blood sugar except for an early and continuing suckling reflex. Serial blood sugars must be taken every fifteen minutes during the first hour of life in order to demonstrate this marked fall. This is in sharp contrast to the fall in blood sugar in the normal newborn, which also falls rapidly, but to not nearly as low a level as that observed in the newborn of diabetic mothers.

Successful management of the newborn baby of the diabetic mother demands that he be cared for as if he were a premature baby irrespective of his actual age. This must be done in spite of the usual oversize and overweight. Prematurity is too often overlooked because of the baby's excessive size and weight.

Meticulous care, therefore, must be accorded the clearance of the upper respiratory tract by postural drainage, adequate pharyngeal and tracheal suction, maintenance of body heat, and oxygenation by immediate transfer to an adequately equipped incubator. This will prevent anoxia and loss of body heat. These babies also suffer from a lethargy during the first hours which must be overcome by frequent and continuing mechanical stimulation.

The hypoglycemia shown to be present in the first hour of life should be prevented by prompt feeding during this period. This may be done by the administration of a few drops of 50 per cent glucose solution, every thirty minutes during the first two hours. It has been observed that the baby has increased suckling action when the blood sugar is low and the glucose solution may be administered readily by a medicine dropper. After this period, breast milk, $\frac{1}{2}$ to 1 ounce, should be alternated with a similar amount of 5 per cent glucose every two hours during the first day of life. These may be given by dropper or by bottle, whichever is more convenient. Regular feedings are given every four hours beginning the second day. Thus, by overcoming anoxia, lethargy, and hypoglycemia, which are the three great dangers to the newborn child of a diabetic mother, the overwhelming majority of these babies can and should be saved.

Lactation

For the most part lactation is not satisfactory in diabetic women, and breast feeding is rarely adequate. The occasional diabetic mother who can and does nurse her baby presents no special problem. The necessary increased intake of food rarely causes more than minor changes in the total diabetic management.

Evaluation of Future Pregnancies

The manner in which the diabetic woman reacts to the problems arising during pregnancy, labor, and the puerperium should be a helpful guide in the evaluation of the desirability of further pregnancy. When this is added to the evaluation of the diabetic woman relative to pregnancy as previously outlined, the problem of permission or interdiction of future pregnancy becomes a simpler one.

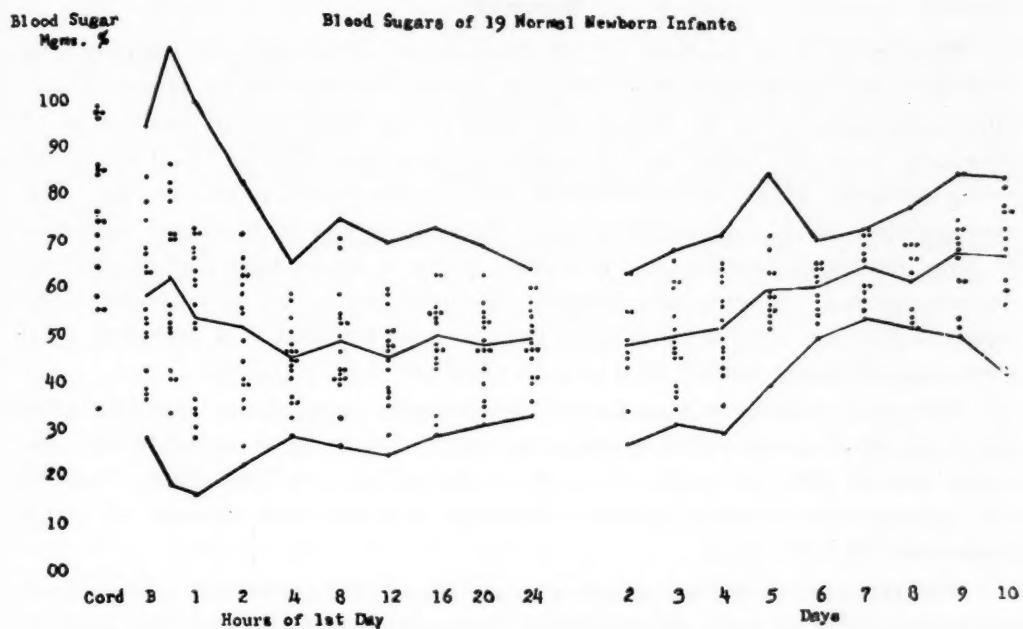


Fig. 1.—The dots represent individual values. The upper line represents the maximum values for each time interval, the middle line represents the mathematical mean. The lower line represents the minimum values for each time interval.

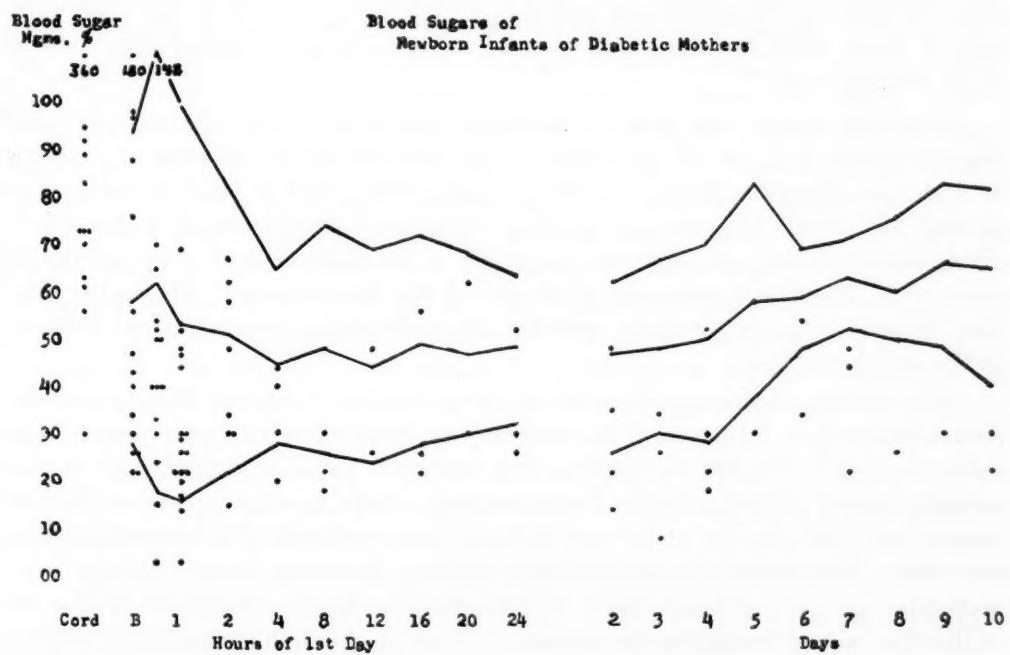


Fig. 2.—The dots represent individual values for newborn infants of diabetic mothers. These are plotted against the maximum, mathematical mean, and the minimum values of the "normal" infants of nondiabetic mothers from Fig. 1.

Note.—Most of the readings are below the average line of the normal curve and a considerable proportion are under the minimum found in babies of nondiabetic mothers.

Summary

This study is an analysis of 163 pregnancies of 52 diabetic patients who were delivered at Michael Reese Hospital during the past fifteen years. Sixty-nine pregnancies occurred before the onset of the diabetes and resulted in 13 abortions (18.8 per cent) and 56 viable pregnancies with 52 (93.0 per cent) living children, 3.5 per cent stillbirths, and 3.5 per cent neonatal deaths. The average birth weight was 3,939 grams. Thus there was an increased incidence of large babies, stillbirths, and neonatal deaths in babies born during the pre-diabetic period. Twenty-two pregnancies occurred in 14 patients after the onset of diabetes but not under our care. These resulted in 4 previable fetal losses and 18 viable babies, of whom 13 (72.2 per cent) survived.

Fifty-two diabetic women had 70 pregnancies while in our care and after the onset of diabetes. Eleven pregnancies (15.7 per cent) ended before viability, and 53 (89.8 per cent) of the 59 viable babies were born alive. Two did not survive the neonatal period. Thus the over-all fetal salvage of viable babies was 86.4 per cent.

The reported increased dangers to the fetus of the diabetic woman from marked increase in fetal abnormalities, malposition, hydramnios, and toxemia were not found in this series. Major fetal abnormalities occurred in only one baby; malpresentation, i.e., breech presentation, occurred in only 7 (11.1 per cent), which is not above the usual increased incidence of breech presentation prior to term; hydromnios was found in 6 (9.5 per cent). It is therefore difficult to agree with the statement that a "normal obstetric course is so rare as to be conspicuous."²⁵

Cesarean section was used to terminate pregnancy in 33 (56 per cent) and vaginal delivery in 26 (44 per cent). The decision as to the type of delivery is a simple obstetric problem. The primigravida, with a long closed cervix, is best delivered by cesarean section. The multigravida with a dilated or dilatable cervix is best delivered vaginally after induction of labor by simple rupture of the membranes and drainage of the liquor amnii. Excessive fetal size, intact cervix, or previous cesarean are indications for abdominal delivery in the multigravida.

The decision as to the time of delivery depends upon the history and the determination of fetal size. In general the fetus of a diabetic woman will achieve a size of 3,300 to 3,700 grams between the thirty-sixth and thirty-seventh weeks of pregnancy. Unfortunately, there is no accurate method of measuring fetal size in utero nor is there any yardstick for measuring fetal maturity. The danger of intrauterine death of the fetus from "diabetic post-maturity" is ever present after the thirty-fifth week. Analysis of the six stillbirths is convincing in this respect. Two of these infants were oversized and died in utero in the thirty-eighth week of pregnancy and the third died during delivery as a result of the delay caused by impacted shoulders. This oversize fetus weighed 5,216 grams. These 3 might have been saved by early termination of pregnancy if more attention had been paid to the fetal oversize.

The placentas of 10 diabetic women were carefully studied by multiple sections and multiple staining methods in an attempt to explain this diabetic postmaturity. There was some evidence of edema with degenerative changes in the villi in 3, varying degrees of infarction in 4, and calcification in 5. Excessive connective tissue was not found. These changes did not vary either qualitatively or quantitatively from those found in placentas of nondiabetic patients.

The incidence of toxemia of pregnancy was 10.2 per cent. The 6 instances of toxemia were classified as mild in 3 and moderate in 3. None were severe. No sex hormone therapy was used in any of the patients in this entire series. Careful evaluation of the confusing literature on this subject together with the results here reported would seem to offer the conclusion that it is unnecessary to subject pregnant diabetic women to the routine of continuous and increasing doses of any type of sex hormone in the light of our present knowledge.

Last, there was no evidence of hypoovarianism in any of our patients. All menstrual histories were within normal limits. No patient complained of periods of amenorrhea and/or sterility. The total fertility rate after the discovery of the diabetes was 1.8. Undoubtedly there will be additional pregnancies in this group of patients in the future which will further increase the fertility rate during the diabetic years.

Premature vascular aging in the diabetic should be a contraindication to pregnancy. When pregnancy is permitted, meticulous care is necessary for the successful management of the diabetes throughout pregnancy, labor, and the puerperium. The diabetic diet must be regulated carefully and constantly with prompt modification for those conditions of pregnancy which have a tendency to upset the normal prescribed intake of food. These include hyperemesis gravidarum, toxemias of pregnancy, the period preceding and during induction of labor, labor and cesarean section, and finally the puerperium.

During pregnancy the insulin of choice is protamine zinc insulin because of its longer action. The amount necessary to keep the patient in metabolic balance may be the same as in the nonpregnant state but in some instances there is need for an increase in dosage and for some the usual dosage must be decreased. The amount used should be sufficient to prevent acetoneuria, to maintain blood sugar at a lower level, to reduce the glycosuria, and finally to give the patient a sense of well-being. This latter can be accomplished best by permitting a slight amount of glycosuria, i.e., up to 15 Gm. per 24 hours, thus avoiding the risk of recurrent episodes of hypoglycemia. The maintenance of a sugar-free urine is usually not desirable.

The amount of insulin necessary varies with each individual patient and from time to time throughout the pregnancy. Adequate dosage can be judged only by the results achieved. There is no other yardstick.

The insulin must be changed to regular insulin whenever complications, such as hyperemesis gravidarum, toxemia, or contraindications to regular food intake arise. It is advisable to switch to regular insulin three to seven days before cesarean section or induction of labor, for the duration of the delivery

and the immediate puerperium. Thus the action resulting from a depot of long-acting insulin is avoided at a time when the food intake must, of necessity, be variable. The regular insulin should be given in divided doses and before each meal, and the dose should be regulated by the glycosuria, the blood sugar levels, and the presence of ketosis. The same type of controls should be used whenever parenteral feedings are required.

The effect of the maternal diabetes upon the newborn infant was studied. Serial blood sugar determinations were made at frequent intervals upon 19 newborn infants of nondiabetic women as a basis of comparison with a series (20) of babies of diabetic mothers. The blood sugar of the baby of a diabetic mother falls more rapidly (within one hour), falls lower, and returns to normal more slowly.

Successful management of the newborn baby of the diabetic mother demands that he be cared for as if he were a premature baby regardless of his actual age, size, and weight. The three real dangers are anoxia, lethargy, and hypoglycemia. Anoxia is prevented by careful clearance of the respiratory passages and oxygen administration. Lethargy is overcome by frequent external stimulation during the first hours of life. The hypoglycemia is treated by frequent administration of 50 per cent glucose solution by medicine dropper during the first few hours. By these means the overwhelming majority of babies can and should be saved. It is, therefore, confirmed that "fetal deaths are exceptional if the diabetes is well controlled and there is good obstetric management" (Hurwitz and Irving).²⁶

Conclusions

1. Careful diabetic management throughout pregnancy and adequate prenatal care without any form of sex hormone therapy, when coupled with individualization in the time and method of the termination of the pregnancy, yield excellent results.
2. The lethargic, oversized, and overweight baby must be treated as if he were a premature baby. Such a baby demands special care.

The authors wish to thank Dr. Rachmiel Levine and Dr. Henry Guterman of the Department of Endocrinology for their advice and assistance in the preparation of this manuscript and Dr. Carl D. Strouse of Los Angeles, Calif., for his study of the blood sugar of normal mothers and their newborn infants.

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Discussion

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—This report records, as far as I am aware, the lowest figure for fetal loss in diabetic pregnant patients yet announced. In presenting their work the authors quite properly devote a considerable portion of their paper to a discussion of the two most controversial issues in this field today, namely, the place of endocrine therapy in the management of the diabetic gravida, and the place of abdominal delivery.

In regard to hormone treatment, the authors consider with great care the theories upon which endocrine management of this condition is based, and point out the manifold weaknesses of the theoretical concepts which underlie such a program. This aspect of the question might be expanded, but if it could be shown that the clinical results for the baby and mother which can be achieved by endocrine therapy are better than those without it, then I am sure we would be willing to overlook any shortcomings in the theoretical basis of this program and hail endocrine therapy in the diabetic gravida as an important step forward. The question is: Are the results any better with hormone therapy in diabetes in pregnancy? It would be desirable in trying to answer this question to be able to base our conclusions on some large number of cases treated by hormone therapy in which both the diabetic and obstetric management were meticulous beyond question. Just such report was published in the November, 1949, issue of the *Journal of the American Medical Association* by Dr. Priscilla White. She reported 439 cases of diabetes complicated by pregnancy, managed by her throughout, with 78 fetal deaths. The mortality rate—stillbirth and neonatal—was 18 per cent and the incidence of cesarean section was 68 per cent. In evaluating this figure of 18 per cent, let us recall that the figure which the present authors report is 13.6 per cent. Let us also recall that some years ago Hurwitz and Irving reported a figure of 15 per cent without endocrine therapy. Others have reported figures of 18 per cent without endocrine therapy. In summary, there is not a shred of evidence, as far as I know, to document the belief that endocrine treatment of diabetes offers any advantage to either the mother or the child. And when it is remembered as well that the theoretical basis for this concept leaves much to be desired, it would seem high time that this concept be discarded into the limbo of discredited theories despite the aggrandizement it has received in the literature.

In regard to abdominal delivery the situation is different because experience shows that the liberal use of cesarean section is essential if we are to obtain the best results for the infant. It is our custom to admit the diabetic gravida three weeks before delivery and carry out careful evaluation of the situation. As a rule, the following are indications for cesarean section: (1) presence of toxemia or evidence of vascular disorder as shown by the eye grounds; (2) a very large baby; (3) hydramnios; (4) previous fetal loss; and (5) diabetes of ten years' standing or more. Under the last named circumstance vascular disease is so common as to make uterine ischemia and fetal death a grave threat. With such a policy it will be found that the incidence of cesarean section in these patients will run from 50 to 75 per cent. As Dr. Reis has pointed out, in multiparas induction of labor is sometimes advisable but I feel that cesarean section is generally to be preferred if we are to achieve the best results.

In conclusion we are indebted to the authors for the following:

1. Hormone therapy is not necessary in the management of the diabetic pregnant woman.
2. The use of cesarean section must be liberalized if the optimum results are to be gained.
3. Meticulous diabetic, obstetric, and pediatric management will yield results that are better than have been achieved in the past.

DR. DUNCAN REID, Boston, Mass.—Dr. Reis has presented in his paper evidence of the wisdom of the conservative treatment of pregnant diabetics. Dr. Reis's results, both maternal and fetal, are the best so far reported. These results have been accomplished by careful diabetic management without supplementary steroid therapy and resorting to operative procedures only on obstetrical indication. Although we may agree in general with the thesis of this paper and the remarks of Dr. Eastman, we believe there are still many aspects of this disease peculiar to pregnancy which remain unanswered. It was our understanding that one of the functions of this paper was to provide an opportunity for a discussion of the many therapeutic problems which this condition presents. Hence, we should like to discuss briefly two aspects of this problem and to make a suggestion.

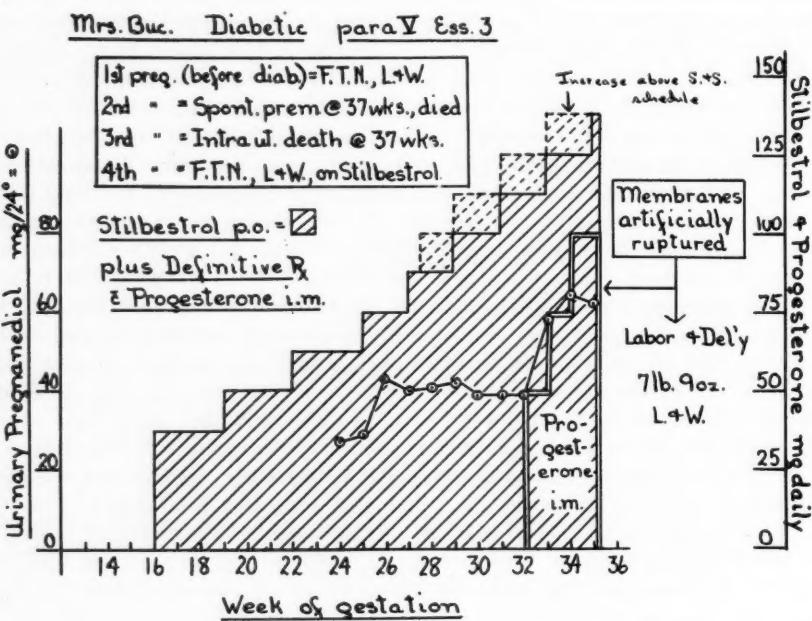


Fig. 1.

The first is concerned with the problem of fetal salvage. It is generally accepted that there is an increased incidence of toxemia with diabetic pregnancies. Because of this and other complications it may be very difficult on occasion to decide the ideal time of delivery for the diabetic patient. In spite of Dr. Reis's excellent results the average fetal mortality rate approximates 20 per cent. Some 15 or 20 per cent of these deaths will occur because of congenital defects, but the residual 80 per cent of the fetal mortality is theoretically salvageable. An analysis of the figures from most reported series of diabetic pregnancies reveals that the incidence of neonatal deaths, due primarily to prematurity, is equal to the stillbirth rate. In an attempt to forestall the latter, it is obvious that many

of the pregnancies were terminated prematurely. To anticipate these fetal accidents of late pregnancy, Dr. Olive Smith has in recent years made determinations of urinary pregnandiol excretion (Venning Method) on nearly all of the diabetic patients at the Boston Lying-in Hospital. Any reduction of pregnandiol values is believed to indicate a decrease in placental steroid output which precedes late pregnancy accidents or the onset of normal labor. A series of observations must be made during the latter half of pregnancy to determine comparatively the extent of this decrease in placental hormone secretion. We should like to present the charts representing success and failure in three diabetic patients cared for at the Boston Lying-in Hospital. In the time allotted we will discuss only the pregnandiol curves which appear in these charts.

In Fig. 1 (Mrs. B.) it will be noted pregnandiol failed to rise from the twenty-fourth to thirty-sixth week, inclusive, even in spite of supplementary progesterone therapy. Values began to fall after the thirty-fifth week. On the basis of these findings, labor was induced with delivery of a living child.

In Fig. 2 (Mrs. F. D.), a failure of urinary pregnandiol to rise normally is observed, followed by a marked decrease during the period of progesterone therapy. Regardless of this warning, labor was not induced and the fetal heartbeat was subsequently lost. We should have anticipated this accident and delivered this patient earlier.

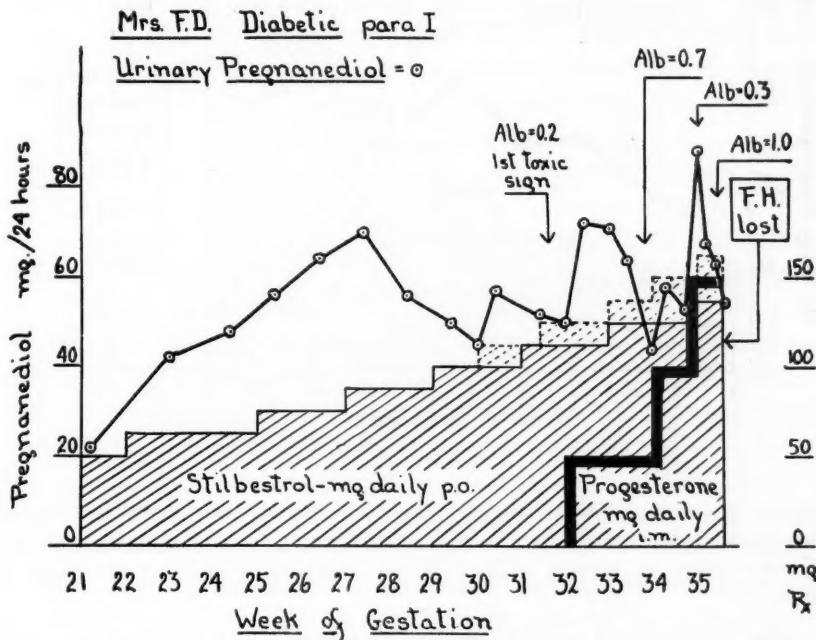


Fig. 2.

Fig. 3 (Mrs. D. G.) shows a case where the pregnandiol curve was essentially normal up to the thirty-fifth week of pregnancy at which time there was a decided fall. Labor was induced with delivery of a living child.

From these determinations we believe Dr. Smith has given us a method whereby alterations in normal placental function can be forecast before the intrauterine existence of the fetus is jeopardized.

The second aspect concerns the type and severity of the diabetes in the patients who make up any particular series. The Boston Lying-in Hospital is assuming the obstetrical care of the diabetic patients of the Joslin Clinic. In the short time we have observed these patients we are impressed with the severity of their diabetes. Dr. Priscilla White of the Joslin Clinic has presented in her recent paper (Am. J. Med., Nov., 1949) a classi-

fication which we believe has merit. Dr. White has attempted to divide her cases into groups on the basis of age of onset, duration of the disease, and changes in the vascular system. It is clear that the latter changes markedly affect the fetal prognosis.

To emphasize further the severity of the diabetes in these patients, one-third of the present group now under prenatal care have had their diabetes before the age of ten years. This suggests that patients with juvenile diabetes may behave quite differently during pregnancy from patients who develop their diabetes during the childbearing age. Certainly an interpretation of the results obtained in this disease must be made in the light of the severity and type of the diabetes under consideration. Hence, we believe that one must not be too critical of hormone therapy for where it has been used the fetal results have been improved.

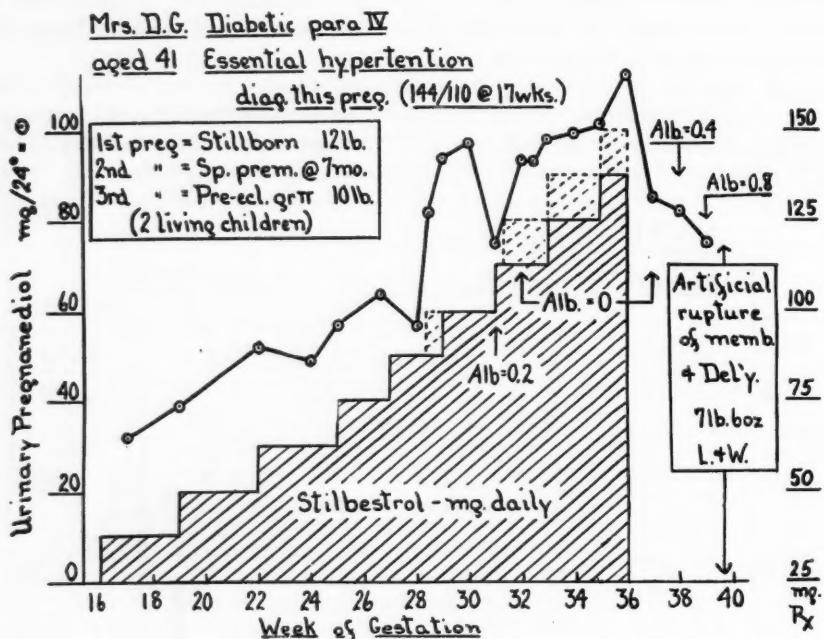


Fig. 3.

Therefore, we should like to suggest that this Society evolve a classification to be used in our various obstetrical clinics. This would allow for a pooling of experience and provide a comparison of results with different types of therapy as used in carefully defined cases.

DR. REIS (Closing).—I want to thank Dr. Eastman and Dr. Reid for their discussions. I have no yardstick, as Dr. Eastman said, for measuring fetal size in utero; at least, at Michael Reese Hospital we have none. We have tried every means known and we have come to the conclusion that we must individualize the patient in every instance and determine as best we can when that pregnancy shall be terminated. In the main, we terminate at the thirty-sixth or thirty-seventh week, occasionally in the thirty-eighth week. As time goes on we have liberalized our indications for cesarean section because we obtain a better fetal salvage that way.

I submit again—because of what Dr. Reid has said about the increased incidence of toxemia—that we found no such increase of toxemia. I submit that we found no marked increase in the incidence of congenital defects, and I submit that there is still no evidence in the literature to show that the administration of estrogen in the form of stilbestrol or any other form stimulates the placental steroid metabolism and increases progesterone manufacture.

THE INACTIVATION OF THE ANTIDIURETIC HORMONE OF THE POSTERIOR PITUITARY GLAND BY BLOOD FROM PREGNANT PATIENTS*†

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Chicago Lying-in Hospital)

PRE-ECLAMPSIA-ECLAMPSIA is associated with an abnormal water, sodium, potassium, and chloride balance. An antidiuretic hormone, presumably from the posterior pituitary gland, has been demonstrated with difficulty in the urine and possibly in the blood of normal and abnormal patients. Dieckmann and Michel^{6, 7} had noted that pre-eclamptic patients showed more marked increases in the systolic blood pressure after small injections of solution of posterior pituitary extract than hypertensive and normal pregnant patients. We have been working since 1946 in an endeavor to devise a method for determining the substance concerned with the inactivation of the ADH of the pituitary gland.

This is a preliminary report, but our study shows an interesting parallel with that of Woodbury²¹ and Page,¹⁵ who worked with inactivation of the oxytocic effect of posterior pituitary extracts.

The oliguria of pregnant patients with toxemia has always been a distressing and baffling problem. The antidiuretic effect of the posterior pituitary hormone was first noted in 1913. At the present time, opinion is still divided as to whether the posterior pituitary gland elaborates one hormone with oxytocic, vasopresser, and antidiuretic effect, or several individual hormones with single effects. At any rate, Theobald¹⁸ found the amounts of antidiuretic hormone in the various posterior pituitary products to be very constant.

In 1918, and again in 1933, Hofbauer¹⁰ attributed eclampsia to altered hepatic function and capillary constriction caused by placental syncytial proteins and ferments resulting in hyperactivity of the posterior pituitary. He felt that the oliguria was caused by elaboration of the antidiuretic hormone (ADH).

Although no proof of pituitary antidiuretic effect in toxemia has been shown, it is still seriously considered to be a factor. Theobald¹⁸ found that as little as 0.005 unit of Infundin would cause measurable antidiuresis and that 0.05 unit usually caused a maximum antidiuretic effect. (Infundin is Burroughs Wellcome & Company's brand of posterior pituitary extract and

*This study was supported in part by the Chicago Lying-in 50th Anniversary Research Fund on Eclampsia.

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contains 10 oxytocic and 10 pressor and antidiuretic units per 1 ml.) He found that pregnant females at term responded in similar fashion to the other controls including males. Samaan¹⁷ found individual variation in the threshold antidiuretic dose required in dogs ranging from 0.000005 ml. to 0.15 ml. of Infundin to obtain antidiuretic effect—an increased specific gravity and chloride concentration in the urine. He found that the threshold dose in each experimental animal was constant and was not altered by denervation of the kidney. Posterior pituitary extract was effective in diuresis resulting from saline and dilute urea solutions, but relatively ineffective in diuresis produced by concentrated urea solution. Wakim and co-workers²⁰ noted a marked decrease in the renal blood flow in the glomerular tufts of frogs after intravenous injection of Pitressin.

In 1945 Pickford¹⁶ concluded that the ADH was made in the pars nervosa of the hypophysis under direct control of the central nervous system by impulses transmitted along the hypophyseal-hypothalamic tracts and that somewhere on this route the impulses depend on acetylcholine for their transmission. Verney¹⁹ was of the opinion that the posterior pituitary accounted for 95 per cent of the natural antidiuretic substances. He found that Adrenalin, Tyramine, and insulin caused a rapid and fleeting antidiuresis with a brief reduction in the renal blood flow. He noted a characteristic antidiuresis resulting from posterior pituitary extract which was less abrupt in onset and more prolonged. He found a similar antidiuresis following moderate arterial hemorrhage, dehydration, short-lived muscular exercise, and emotional stress and considered it due to the pituitary. He injected hypertonic solutions into the carotid artery and concluded that there are osmoreceptors in the vascular bed of the internal carotid which are important in the release of posterior pituitary hormone upon stimulation by hypertonic solutions.

Lipschitz and Stokey¹⁴ have shown that morphine and phenobarbital have an antidiuretic effect due in part to liberation of the ADH and in part to effects on renal innervation and a humoral antidiuretic factor. Birnie and co-workers^{2, 3, 4, 5, 12} reported an antidiuretic substance in the blood of normal rats which was markedly increased by adrenalectomy and absent following hypophysectomy. They believed that this substance was ADH and acted by increasing tubular resorption since the normal creatinine clearance tests were taken as an indication of relatively normal glomerular filtration.

Dieckmann^{6, 7, 8} noted that pregnancy serum was antagonistic to the pressor activity of posterior pituitary extracts. Larson¹³ showed an enzymatic destruction of the pressor effect and suggested that aminopolypeptidase of the tissue eruptases was the inactivator.

Von Fekete⁹ in 1930 first showed a reduction in the oxytocic effect of posterior pituitary hormone by incubation with pregnant blood. In 1946 Woodbury and co-workers²¹ found that oxytocin was inactivated more rapidly when incubated with blood of women from the fifth month of pregnancy to the first week post partum than by the blood of nonpregnant controls. The blood of toxemic patients inactivated the pitocin as rapidly as that of normal patients. Page¹⁵ demonstrated that crystalline chymotrypsin, aminopolypeptidase, angiotonase, and several other enzymes could destroy Pitocin; however, he felt that another enzyme which he called "pitocinase" was primarily responsible. Page¹⁵ and Aragon¹ could find no correlation between pitocinase levels and toxemia. All of these tests were made using uterine or intestinal strips from animals or the human uterus.

Heller and Urban¹¹ in 1935 found that the antidiuretic hormone was inactivated in vivo and in vitro. In vitro it seems the hormone is rapidly inactivated by adsorption when incubated with blood and tissue suspensions.

This process is reversible by desorption. Each tissue was found to have a specific adsorbing capacity. In addition there is slow and irreversible inactivation by an enzymelike agent. *In vivo*, apparently adsorption is rapid and the hormone is eliminated by renal excretion and subsequent enzymatic destruction of the adsorbed hormone.

Method

Immediately preceding the experiment, 20 ml. of blood are obtained from the subject and added to a sterile 50 ml. centrifuge tube containing 5 ml. of 4 per cent weight per volume of sodium citrate. Parke, Davis and Company's Pitressin containing 20 pressor units per ml. is used. Five-tenths ml. of Pitressin is accurately measured and added to 19.5 ml. of saline solution. After mixing, 0.2 ml. of this dilute solution is accurately measured and added to the 25 ml. of citrated blood. Ten ml. of the 25 ml. amount is used so that the final dose is 0.04 unit or 0.002 ml. of Pitressin.

This mixture of citrated blood and Pitressin is then incubated in a water bath for one hour at 38° C. Following incubation, the blood is centrifuged for 20 minutes and 10 ml. of plasma are drawn off for subsequent use in the test subject. Sterility must be maintained.

The test subjects have been normal patients selected during the first week after delivery or gynecological patients. A diuresis is established and maintained in the subjects by an initial oral intake of 1,200 ml. of water within 30 minutes and 300 ml. at 60 and 120 minute periods for a total of 1,800 ml. The procedure lasts for two and one-half hours and during this time urine specimens are taken every thirty minutes by removal of a clamp on an indwelling catheter and expression of the entire contents of the bladder. Within one hour, the time the 60-minute urine specimen is obtained, the diuresis is well established and the 10 ml. of plasma, which was obtained from the centrifuged blood and Pitressin, is given intravenously to the subject. The effect of the Pitressin is noted on the subsequent urine volumes and on the concentration of chloride, sodium, and potassium (Fig. 3).

The thirty- to sixty-minute urine volume and electrolyte concentrations were given the value of 100 per cent and the other data were converted to their percentage of this value. The chlorides were determined by the Volhard-Harvey method and the sodium and potassium by the Beckmann flame photometer (Figure 4).

Results

No systemic effects were noted in the subjects during this procedure. Twenty-seven patients were used as test subjects, and only one was unable to drink the necessary amount of water. There was no evidence of pressor effect resulting from the minute doses of Pitressin.

Five-tenths unit of Pitressin was initially used and the resultant antidiuresis lasted for two and one-half to three hours, which was long enough to exhaust the patient. By gradually lowering the amount of Pitressin we arrived at the present dose of 0.04 unit which causes an antidiuresis lasting from 30 to 60 minutes. Serum was initially used for the incubating medium but apparently did not contain a sufficient amount of the inactivating substance, therefore citrated whole blood was used and the plasma drawn off for injection to obviate cross-matching of the blood. Twenty-two such experiments have been completed using this present method. Fifteen were performed with blood from pregnant patients, ranging from the seventh week of pregnancy to the sixth week post partum. There are seven control experiments, four with incubation and three without.

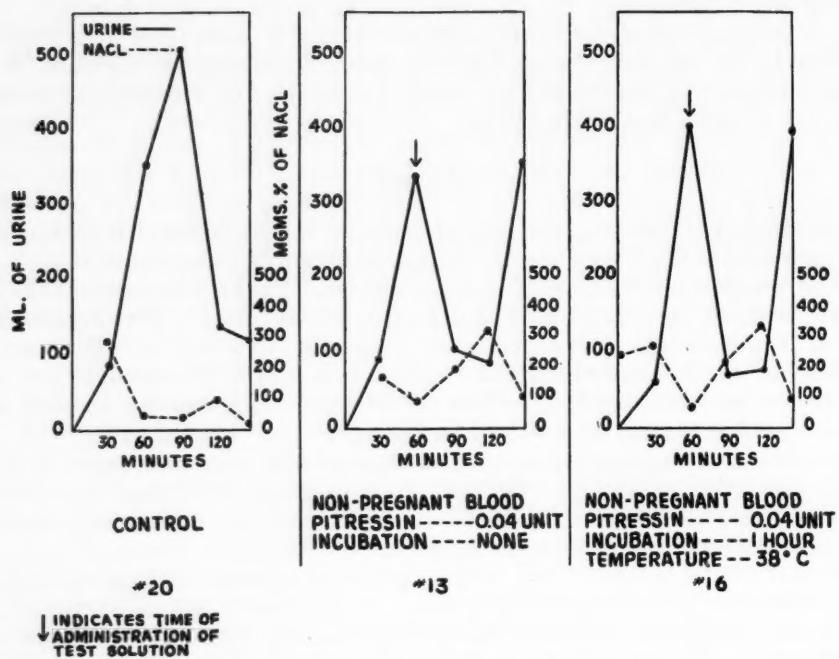


Fig. 1.—Illustration of diuresis due to oral ingestion of 1,800 ml. of water. Inhibition of diuresis and increase in concentration of urine chloride due to the injection of Pitressin.

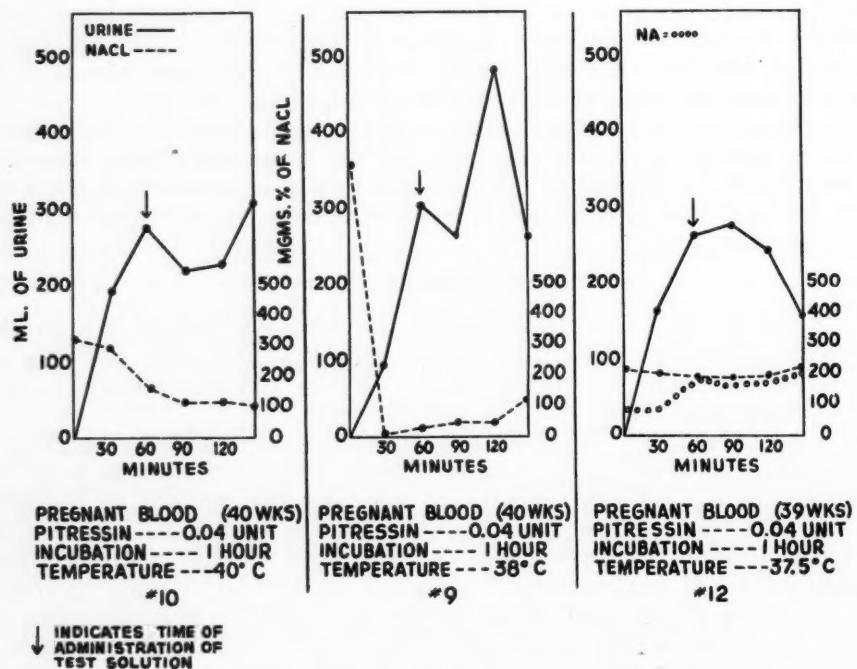


Fig. 2.—The three graphs show varying degrees of inactivation of the Pitressin.

With this method of diuresis the urinary output at the end of an hour is usually in the neighborhood of 300 ml. although several patients had a low output even though they cooperated well. During the subsequent half hour it continues to rise if no Pitressin is injected. When 0.04 unit of Pitressin is given at the sixty-minute level of diuresis, the ninety-minute urine output drops to about 60 ml. If Pitressin and blood from nonpregnant patients are given, with or without incubation, there is a similar drop in output to the neighborhood of 80 to 120 ml. total. However, when Pitressin incubated with blood from patients late in pregnancy is given, this drop in urinary output is considerably reduced or there may be an increased output.

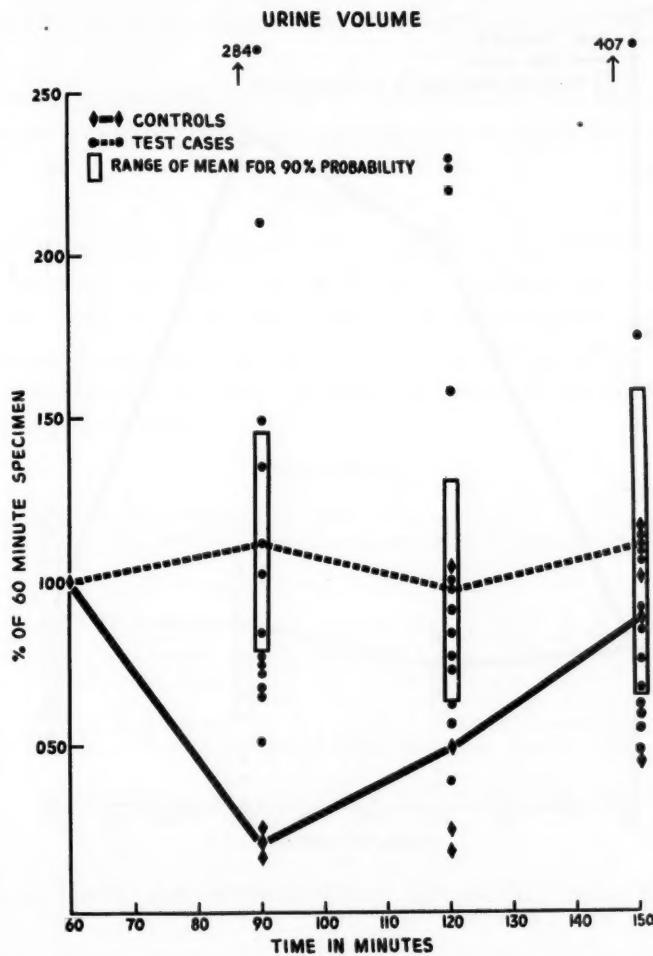


Fig. 3.—Graph of mean urine volumes, showing antidiuresis in control cases and diuresis in test cases.

The first graph in Fig. 1 shows the urinary output curve obtained with 1,800 ml. of water without the administration of Pitressin. The second and third graphs show the usual drop in urinary output at ninety minutes when Pitressin mixed with blood from nonpregnant patients is given. There is a complete lack of inactivation. A similar drop is noted when Pitressin is mixed with blood from pregnant patients and not incubated. In Fig. 2 all three graphs show the relative inactivation of the Pitressin when it is incubated with blood from pregnant patients. There is some inactivating substance in blood

during pregnancy which makes its appearance between the fourteenth and twenty-first weeks, persists throughout pregnancy, and then disappears gradually during the postpartum period. This probably is an enzyme as suggested by Heller and Urban¹¹ and may even be the enzyme which inactivates the oxytocic action of Pitocin described by Woodbury²¹ and Page.¹⁵ This ability of blood in pregnancy to alter Pitressin antidiuretic activity is a phenomenon not previously described.

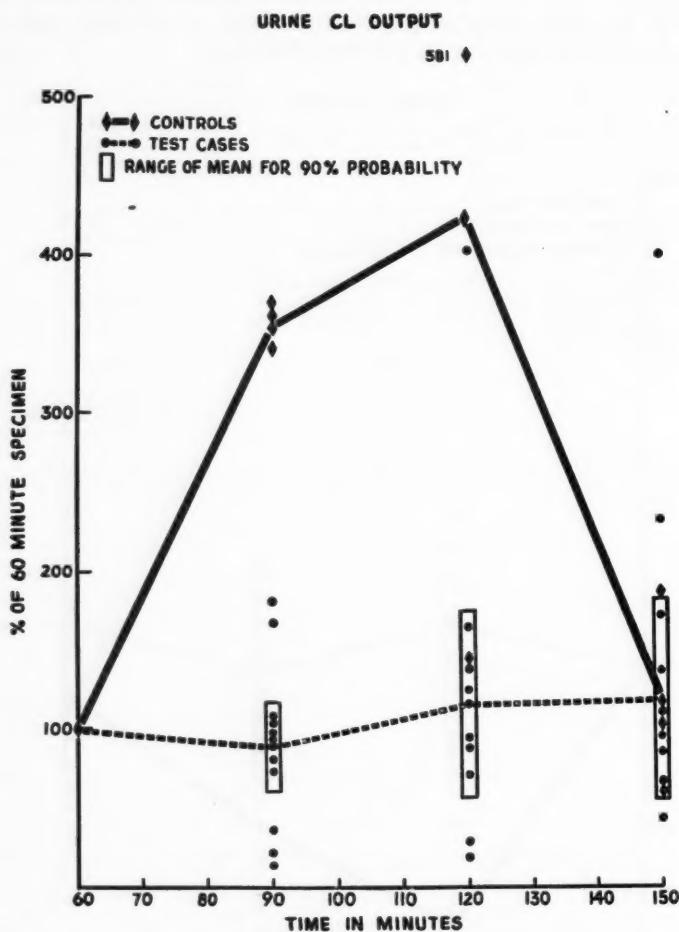


Fig. 4.—Graph of mean urine chloride concentrations showing chloruretic effect in control cases and absence in test patients.

In brief, if we give the sixty-minute urine volumes a value of 100 per cent, we find that the ninety-minute values in the controls are between 17 and 42 per cent, whereas the pregnant blood experiments give us values ranging from 51 to 284 per cent after the fourteenth week of pregnancy (Fig. 3).

In the controls the concentration of chlorides in the ninety-minute volumes is markedly increased, usually around 300 per cent, whereas the chlorides in the pregnant blood experiments are only slightly increased or even lowered, ranging from 15 to 181 per cent. The sodium and potassium levels parallel the results obtained with chlorides (Fig. 4).

In some of the subjects in whom good inactivation of the Pitressin was noted, an injection of a similar dose of Pitressin was given at 150 minutes.

In each instance a drop in urinary output occurred which was similar to that of the controls and indicated to us that the subject would have shown anti-diuresis at the ninety-minute period if the Pitressin had not been inactivated. We also noted that the injection of the plasma from incubated blood without Pitressin caused no appreciable effect.

Comment

These experiments indicate that blood in the latter half of pregnancy has the ability to inactivate the antidiuretic effect of commercial Pitressin. We did not have the opportunity to study any patients during the phase of oliguria. We think that the test is of value in the study of the oliguria of pre-eclampsia-eclampsia.

We are investigating the process of inactivation. As Heller and Urban¹¹ suggested, there probably are two processes: enzymatic destruction and adsorption.

Summary

A simple method is presented for evaluating the antidiuretic effect of solution of posterior pituitary, using human subjects for the experiments.

Our studies indicate that when Pitressin is incubated with blood from patients in the last half of pregnancy, the antidiuretic effect of Pitressin is absent or markedly diminished. Incubation with blood from nonpregnant patients evokes little change.

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Discussion

DR. S. A. COSGROVE, Jersey City, N. J.—The presentation by Dr. Dieckmann and his co-workers to which we have just listened is admirable in the systematized background

for his work, the well-organized bibliography, and the ingenuity and care with which the observations upon which the paper is based were carried out.

It constitutes a report of an originally observed phenomenon, the ultimate significance of which is conceded by the authors to depend on much further work extended to the oliguric phase of toxemias, and effort to determine the process of inactivation. Moreover, it would seem to me that the variability of individuals' reactions shown by the several graphs presented would necessitate the carrying out of the present experimental basis for any future conclusions on a much larger scale than the twenty-seven cases here reported.

Further, it is evident that the effect of the minimal doses of Pitressin used was very transient, even when not inactivated by pregnant blood, and that the total diuresis over a period in excess of two hours exceeded that in control cases. It is obvious that the administration of single doses of any amount does not parallel the constant physiological elaboration of the antidiuretic principle in either health or disease. Further work might perhaps well include repeated doses of Pitressin during the period of observation in an attempt more closely to simulate the physiological production both of pituitary principles and the principle in blood in pregnancy which inhibits the ADH.

Dr. Dieckmann stated in a personal communication to me that he hopes this work may help in the study of the oliguria and anuria of pre-eclampsia-eclampsia. Since there is much doubt of the identity of the pituitary ADH with probable other antidiuretic substances known to occur in toxemia (compare the apparent tendency of pituitary ADH to *increase* chloride excretion with Dieckmann's own finding of the negligible excretion of chloride in severe toxemia), there are many gaps to be filled in before the present contribution can add much to our real knowledge of the oliguria and anuria of toxemias.

But without regard to its place in such eventual knowledge, it may well be of value from another and more direct angle. If, when properly elaborated and standardized, it is found to lend itself as a clinical measure of the difference in behavior of blood from normally pregnant and that from toxemic patients, it will on its own merits per se be a most valuable contribution.

DR. DIECKMANN (Closing).—In our original paper there were twenty-seven cases; thirty more have been added and more work is in progress. I want to mention the work of the van Dyke group because they cannot find the antidiuretic hormone in the femoral blood of experimental animals but after injecting hypertonic saline solution into the internal carotid they can find the ADH in blood from the external and internal jugulars. We have been trying to find the antidiuretic hormone in peripheral blood, but we must obtain it from the internal jugular vein, probably by catheter.

GLOMERULAR FILTRATION RATES, RENAL PLASMA FLOW, AND SODIUM AND WATER EXCRETION IN PREGNANCY TOXEMIA*

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WITH our continued inability to reduce maternal and fetal mortality rates in pregnancy toxemias to zero and with the steadfast defiance of this condition to lend itself to a satisfactory explanation of etiology, the toxemias of pregnancy have issued a major challenge to the field of obstetric investigation. Because of their similarity to the clinical course and termination in certain types of renal disease, this challenge has been met over the years by the utilization of virtually every available test known to the study of the mechanisms of renal function. Many such studies have been introduced in the hope not only that treatment might be improved but also that further information might be obtained which would be of aid in clarifying physiology, etiology, and possibly prognosis.

The kidney, as the possible initial factor and trigger mechanism of the processes involved in the toxemias of pregnancy, has been largely evaluated heretofore through the study of pathologic material presented in the autopsied patient. With the thought that these pathologic processes might be explored in the living patient and in the hope that concrete knowledge might be gained from these processes as they work, studies of the actual physiology of renal mechanisms were carried out in patients presenting the various types of toxemia of late pregnancy.

Anatomically, it is known¹ that, before the afferent arteriole enters the glomerulus, the muscle cells of the media adjacent to the distal convolution of its own nephron are modified, appearing as relatively large afibrillar cells. It seems, for the most part, that the arteriole is invested in a nestlike group of cells embedded in a delicate fibrillar network. While the exact function of this reticulum has not been determined, it has been said to possess glandular activity. However, it is not known whether all afferent arterioles contain it, but it occurs commonly in man. The efferent arteriole contains only circular smooth muscle fibers in its wall and, because of their presence, the degree of constriction or relaxation of these fibers has been felt to control intraglomerular blood pressure. From the physiologic standpoint, the intraglomerular pressure is governed by the arterial blood pressure and by the degree of change in the caliber of the efferent arteriole effected by the circular fibers.

*Presented, by invitation, at the Seventy-Third Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 11 to 13, 1950.

Practically all the routine evaluations of renal function, singly or collectively, such as the PSP test, urea clearance, dilution test, concentration test, blood urea nitrogen, carbon dioxide combining power, serum proteins, and even the urinalysis, have shown no constant correlation with the clinical picture found in the toxemias of pregnancy. Certainly none of these can be considered characteristic of any one group of pregnancy toxemias.

With the idea of determining the renal changes involved in the toxemias of pregnancy, we felt that careful evaluation of renal clearance processes offered a satisfactory approach to the study of the underlying phenomena involved. The observations by Page and Corcoran,² Smith,³ Goldblatt,^{4, 5} Goldring,⁶ and others have already shown that the renal factor plays an important part in hypertensive disease. Coreoran and Page,⁷ Dill,⁸ Chesley,⁹ Taylor and Welsh,^{10, 11} and Kariher¹² have conducted similar studies to evaluate the renal factor in the toxemias of pregnancy.

Renal clearance may be defined as the amount of blood or blood plasma containing the same amount of a substance as is excreted in the urine in a unit of time. A great many substances have been and may be used to determine renal clearance. Some of the more readily available and easily excreted substances such as those normally found in the blood (urea,¹³ creatinine or phosphate) are the more commonly used, but usually consideration of the metabolism of these substances is involved. In addition, other substances^{14, 15} may be introduced directly into the blood stream and their clearances measured.

Subjects and Materials

In an attempt to develop more concrete information as to just what goes on in pregnancy toxemia, measurements of renal function as determined by glomerular filtration rate, renal plasma flow, filtration fraction, and the renal excretion of sodium were performed.

These studies were made on patients in whom a definite diagnosis of toxemia of pregnancy was made. The patients were grouped according to the classification proposed by the American Committee on Maternal Welfare. All patients were hospitalized for a significant toxemia of pregnancy and, during their hospitalization, presented the signs and symptoms of pregnancy toxemia. In addition, each of these patients was again evaluated at least six weeks after delivery, and the final classification of the toxemia determined from antepartum, postpartum, and late puerperal findings, as well as on data derived during the pregravid period where available. Thirty such patients form the basis for this presentation. Nine cases were classified as mild pre-eclamptic toxemias, thirteen were severely pre-eclamptic, and eight were classified as essential hypertensive toxemias.

Methods

No food or liquids were allowed during the twelve hours preceding the study. Immediately prior to the study, the patients were given 600 c.c. of water to drink. During the two days prior to the determination of each test, the patients were placed on a known low-sodium intake not exceeding 800 mg. per day and each patient was given 17.6 Gm. of sodium chloride daily over the 48-hour period ending one day prior to the test. At the time of the actual determinations, the patients were catheterized, the bladder drained, and a mul-

triple-opening catheter left inlying for the subsequent collection of urine specimens. The first specimen was discarded. A 5 per cent dextrose drip was started in one arm with a three-way stopcock inserted between the glass adapter and the needle to facilitate removal of blood specimens. The first blood sample of 12 c.c. was taken from the other arm with a No. 18 needle. This needle remained in the vein and the tubing from the infusion pump attached, thus starting the sustaining solution of mannitol or inulin, para-aminohippurate and 5 per cent dextrose in water. A priming dose of 50 c.c. of 25 per cent mannitol or 30 c.c. of 10 per cent inulin was introduced intravenously, thus bringing the body to a state of equilibration.

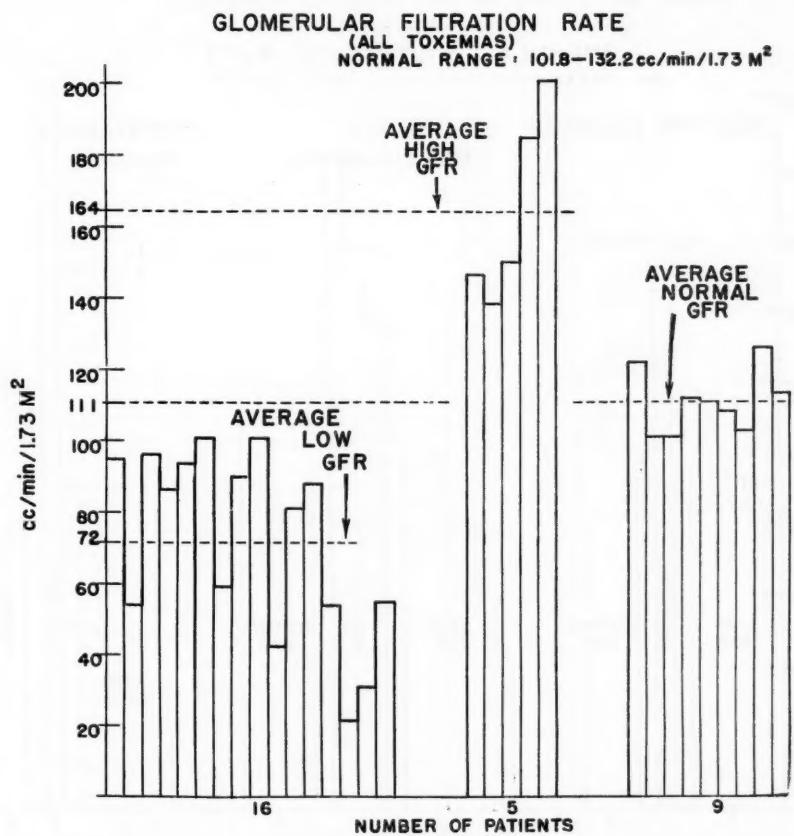


Fig. 1.

The bladder was drained completely every twenty minutes and then washed to insure complete collection of urine. Each collected urine specimen was measured and saved for laboratory analysis. At the completion of each urine collection, blood samples were taken.

Blood pressure and pulse were closely observed and recorded. The exact time of collection of each specimen was recorded, as well as a complete notation of the patient's reaction and any unusual events in the procedure. The number of cubic centimeters of sustaining solution injected was noted for each period, a period consisting of that time between the end of one urine collection, through the end of the next urine collection.

Glomerular filtration rate was measured using mannitol in the earlier group of patients and, in the latter group, inulin was employed for this purpose. Both are polysaccharides and neither is reabsorbed nor excreted in the tubules.

Inulin, or mannitol, when injected intravenously, is soluble in the plasma water, does not combine with the plasma proteins, is filtered with the plasma water at the glomerulus, and is neither added to nor removed from the renal tubular fluid. Glomerular filtration rate, in normal individuals, falls between 102 and 132 c.c. per minute with an average of 117 c.c. per minute. Its clearance is equal to the rate of filtration. In this way, all inulin filtered at the glomerulus is found in the urine. Hence, the amount of inulin found in the urine equals the amount of inulin filtered and in the same amount in the plasma water as the amount filtered through the glomeruli in one minute. The rate of glomerular filtration can thus be determined since the amount and concentration of inulin are known in one minute's filtrate.

GLomerular Filtration Rate

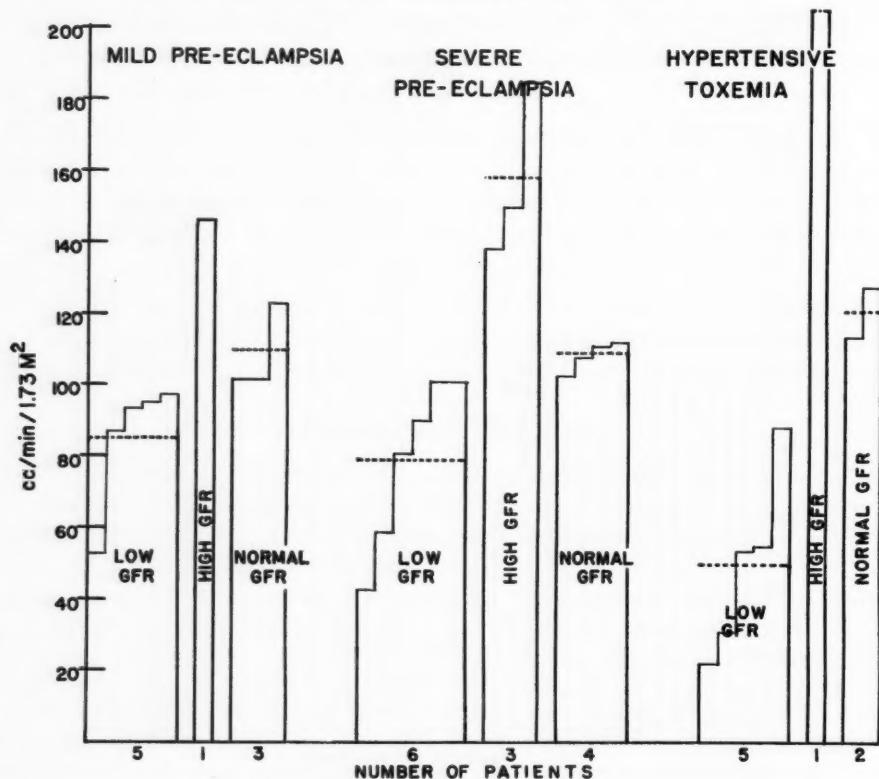


Fig. 2.

The renal plasma flow was measured utilizing *p*-aminohippurate. A certain portion of the total amount of *p*-aminohippuric acid injected is bound to the plasma proteins while the remainder is in free solution in plasma water with which it can pass through the glomeruli with the glomerular filtrate. At low plasma levels, practically complete removal of this substance occurs. At the proximal convoluted tubule, *p*-aminohippuric acid enters the cell and is transferred through it by a physiochemical mechanism. It is then excreted by the tubules into the tubular fluid and excreted in the amount equal to the concentration in the plasma water as the plasma circulates past the tubules during the period of excretion. As shown by Goldring and Chasis,⁶ *p*-aminohippuric acid is practically completely removed from the renal arterial blood in one circulation through the kidneys, and the clearance of these substances is identical

with the rate at which blood itself is circulated through the kidney. Thus, the renal excretion of *p*-aminohippuric acid occurs by both glomerular filtration and tubular excretion.

Filtration fraction was computed in these patients and is that quantity of plasma filtered at the glomerulus related to the total renal plasma flow. This is obtained by dividing the rate of glomerular filtration by the renal plasma flow and is expressed in percentage.

Calculation of the data was made according to the methods described by Goldring and Chasis.⁶ Throughout our calculations, all data have been corrected to 1.73 M² of ideal body surface.

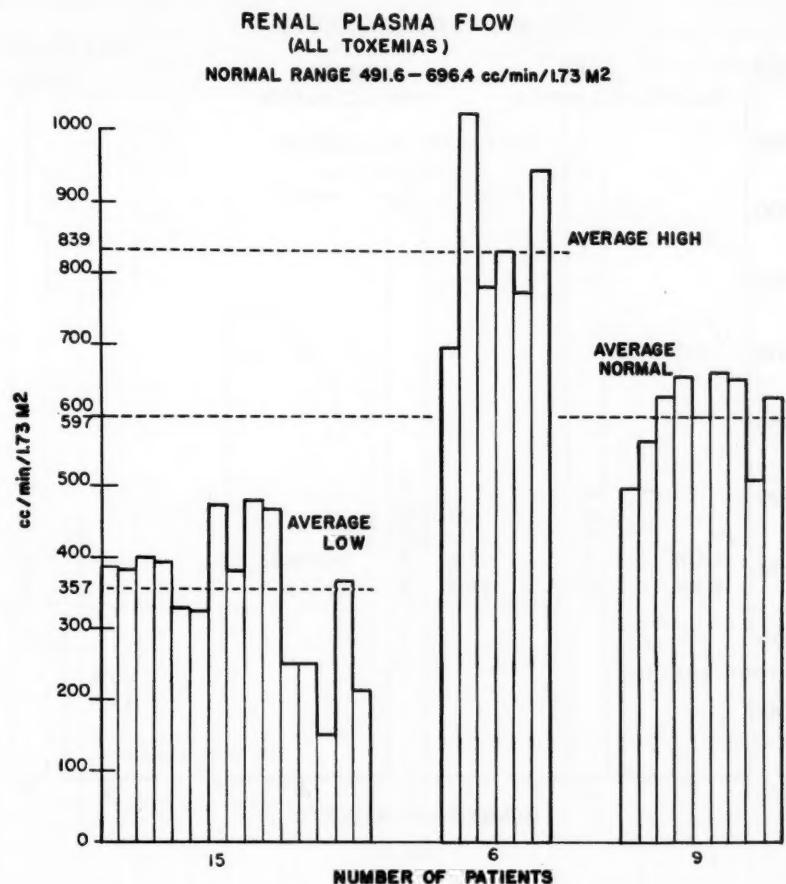


Fig. 3.

Smith and co-workers,¹⁶ using an infusion of 200 mg. per minute of inulin to maintain a 100 to 150 mg. per cent blood level in normal patients, reduced the amount according to kidney damage. Dill and associates used an infusion of 120 mg. per minute which would result in a blood level of 60 to 80 mg. per cent. In our patients, we varied the inulin concentration of our solution according to the surface area of the patient in order to maintain a blood level of 25 to 35 mg. per cent. Such concentration controls the inulin output in the urine and this precludes any danger of crystallization, such as would occur at the higher levels used by the majority of other investigators.

All testing solutions were introduced intravenously, using a constant-speed infusion pump, especially designed and calibrated for this purpose, thus

permitting the administration of the solution at a rate of 1 c.c. per minute. The use of a constant-infusion pump seems to facilitate the control of concentration of the reagents in the blood. In most reports, apparently the substances were introduced by means of a controlled continuous intravenous drip.

Taylor, Welsh, and Wellen averaged at least three collection periods for each clearance and, in addition, two to four clearance tests were made on each patient. Three collections were averaged by Dill and associates, but Kariher and George do not mention the number of collection periods nor do they state the number of blood samples taken during a given test. In our study, an average of 3 to 6 collection periods for each clearance was made.

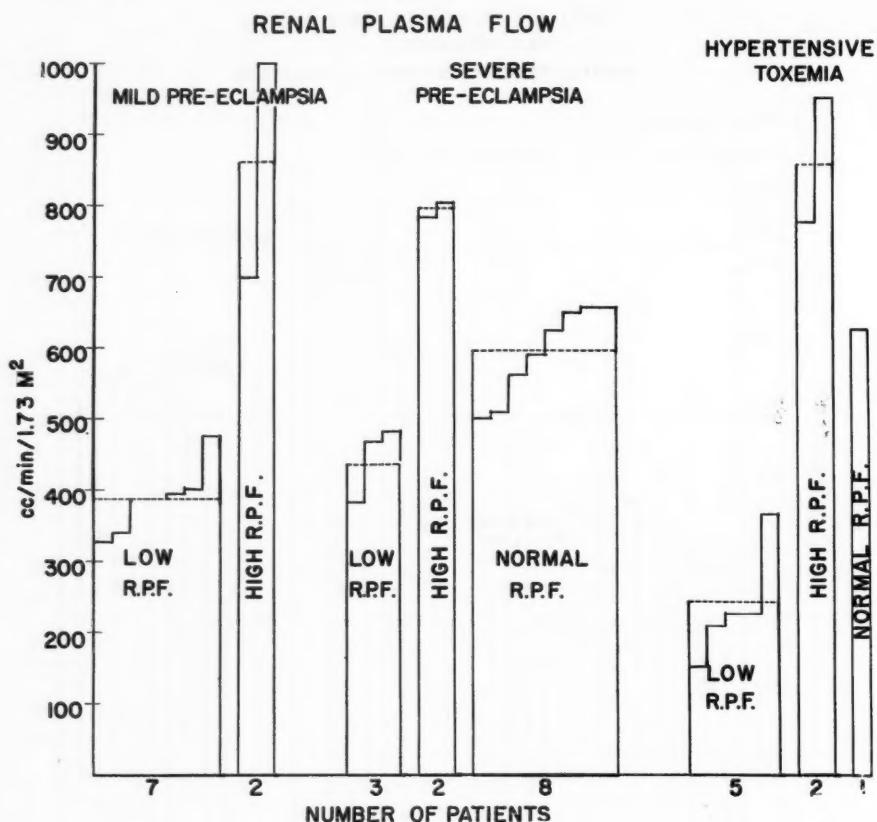


Fig. 4.

Two or three venous blood samples were taken by Taylor and others, during the clearance periods. Dill and his co-workers took blood samples in the middle of the first and in the middle of the third periods and interpolated to the middle of the second period. We took blood samples at the end of each collection period and interpolated to the middle. Since it is sometimes difficult to maintain a constant concentration even with the use of a constant-speed infusion pump, it was felt advantageous to take blood samples at regular and frequent intervals. We feel, therefore, that our technique insures the maintenance of an accurate blood concentration at any one time.

In order to obtain and to maintain high urine flow, Taylor, Welsh, and Wellen used sodium sulfate, sorbitol, or mannitol as a diuretic. In their determinations, urine volumes falling below 2 c.c. per minute were rejected. Dill and associates varied the collection period in inverse proportion to the volume of urine flow in order to secure 80 to 120 c.c. of urine from each collection period.

Flows less than 1 c.c. per minute were rejected. Even though it may seem desirable to maintain urine flow at an elevated level in order to insure the extraction of all the urine with greater accuracy, we have made no such attempt to increase urinary flow with diuretics. In our determinations, periods were exactly twenty minutes long and no minimum urine volume was set. However, there were only two instances in our group of cases in which the urine volume averaged less than 2 c.c. per minute.

Results

We have grouped our observations, for the most part, into three categories and have tried to note relationships of each group to urine output and to sodium metabolism. These three divisions are: (1) observations of glomerular filtration rates, (2) observations of renal plasma flow, and (3) observations of variations in the filtration fraction.

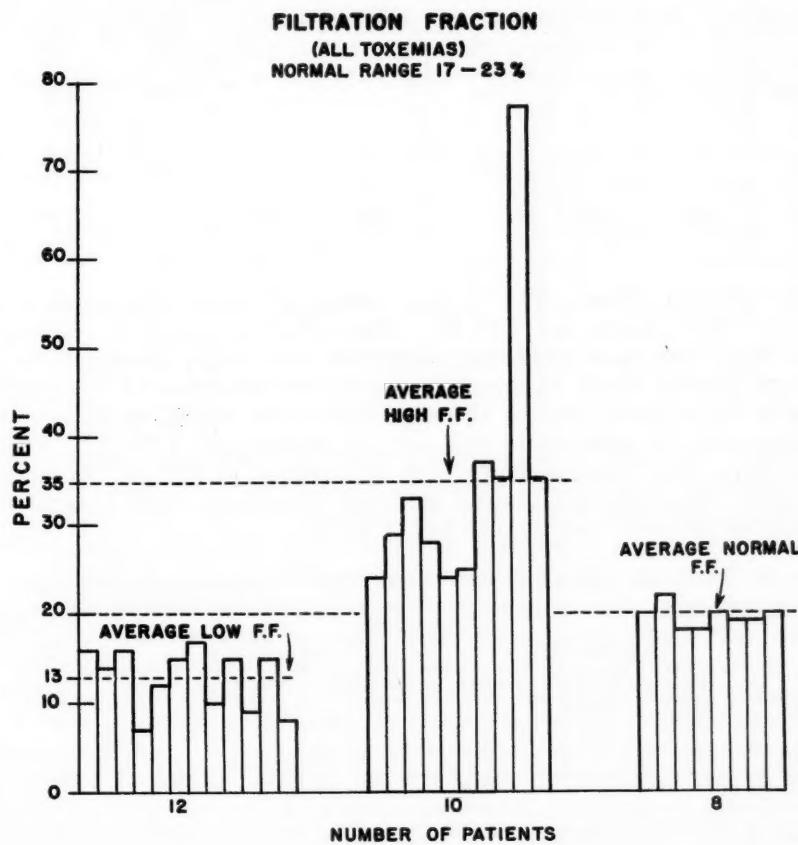


Fig. 5.

Glomerular Filtration Rate.—The glomerular filtration rate as determined by mannitol or inulin clearance in these pregnancy toxemia patients averaged 102.3 c.c. per minute per 1.73 M^2 of body surface for the entire group. In accord with the majority of recorded observations, as shown in Table I, the largest single group of our patients with pregnancy toxemia (Fig. 1) revealed evidence of lowered glomeruli filtration. Sixteen per cent of our patients showed evidence of glomerular filtration rates above normal levels with an average of 164 c.c. per minute, while 30 per cent presented normal glomerular filtration rates with an average of 111 c.c. per minute.

Fig. 2 considers each type of pregnancy toxemia and the determination of glomerular filtration rate in each of these. It was found that the majority of each type of toxemia was characterized by lowered filtration rate at the glomerulus. In considering those individuals with specific toxemia of pregnancy, we find that the average glomerular filtration rate falls just within the lower limits of normal. Even in the hypertensive group, there was only one in whom glomerular filtration was increased, and this, we feel, was due to profound shock which occurred during the test.

TABLE I. GLOMERULAR FILTRATION RATE (102-132 C.C./MIN./1.73M.²)

	PRE-ECLAMPSIA						HYPERTENSION	
	ANTEPARTUM			POSTPARTUM			ANTEPARTUM	POSTPARTUM
	MILD	SEVERE	COMB.	MILD	SEVERE	COMB.		
Kariher and George ¹²	109	115		121	138		145	118
Dill et al. ⁸			84.0				105	87
Coreoran and Page ⁷			90				102	106
Taylor et al. ^{10, 11}			114				132	97
Present Study	103	103		102	97.1		100	

Renal Plasma Flow.—The normal range of renal plasma flow is 491.6 to 696.4 c.e.⁶ per minute per 1.73 M². The values obtained by the majority of observers show that most pregnancy toxemias have renal plasma flows that fall within these normal limits (Table II). In the consideration of our toxemias as a whole (Fig. 3), exactly half of these patients were found to have a low renal plasma flow with an average of 357 c.e. per minute per 1.73 M². Six patients presented high renal plasma flows with an average of 839 c.e. per minute per 1.73 M² while nine patients showed evidence of normal renal plasma flow with an average of 597 c.e. per minute per 1.73 M².

TABLE II. RENAL PLASMA FLOW (492-696 C.C./MIN./1.73M.²)

	PRE-ECLAMPSIA						HYPERTENSION	
	ANTEPARTUM			POSTPARTUM			ANTEPARTUM	POSTPARTUM
	MILD	SEVERE	COMB.	MILD	SEVERE	COMB.		
Kariher and George ¹²	579	531		553	612		613	521
Dill et al. ⁸			680				482	515
Taylor et al. ^{10, 11}			683				603	571
Coreoran and Page ⁷			464				417	
Present Study	536	593					523	446

In evaluating our patients according to the clinical classification of the disease (Fig. 4), it was found that the majority of patients among all types of toxemias presented renal plasma flows of low magnitude. Particularly was this true in the hypertensive group, as anticipated, but in mild pre-eclampsia as well.

Filtration Fraction.—The filtration fraction in pregnancy toxemia, according to the majority of investigators, is reported as being characteristically low (Table III). Particularly is this true in their observations among antepartum pre-eclampsia patients. In our series, filtration fraction, during either the antepartum or postpartum period, was found to be within normal limits in each instance of true toxemia of pregnancy. However, in the hypertensive group, we found characteristically elevated filtration fraction, a feature quite well in accord with the majority of observations. In considering all our patients (Fig. 5) and the relation of the filtration fraction to normal values, we find that the great majority of our patients present evidence of a lowered filtration fraction when we group all of the toxemias together and do not attempt to isolate them as to the type of toxemia. Among those with an elevated filtration fraction, the average level was found to be 35 per cent.

TABLE III. FILTRATION FRACTION (17-23 %)

	PRE-ECLAMPSIA						HYPERTENSION	
	ANTEPARTUM			POSTPARTUM			ANTEPARTUM	POSTPARTUM
	MILD	SEVERE	COMB.	MILD	SEVERE	COMB.		
Kariher and George ¹²	19.0	21.4		21.9	21.9		23.6	24.8
Dill et al. ⁸			16.7			22.8	22.8	23.4
Corcoran and Page ⁷			16.2			21.3	25.3	24.9
Taylor et al. ^{10, 11}			16.7			22.2	17.3	25.7
Present study	22.9	19.4				19.9	25.4	

In regrouping these patients according to type of toxemia (Fig. 6), it is seen that those with mild pre-eclampsia presented an equal number with low filtration fraction and normal filtration fraction, while the hypertensive group presented a characteristically low filtration fraction.

In comparing glomerular filtration rate to filtration fraction (Fig. 7), an increase in the glomerular filtration rate without a simultaneous increase in renal plasma flow results from an increase in the filtration fraction. This might well be considered to be on the basis of: (1) glomerular endothelial damage with resultant increase in permeability of the glomerular capillary, or (2) possibly to the presence of efferent arteriolar constriction with relaxation at the afferent arteriole. It is seen in this latter group that where a distinct lowering of the filtration fraction occurred, the patients presented the more severe types of toxemia. This group may well comprise those destined to present ultimately evidence of latent disease, primarily of the hypertensive type. We plan a continued follow-up on these patients in order to determine whether or not we may reach a safe conclusion as to prognosis at the actual time when we are evaluating these patients' renal function during the antepartum period.

Water and Sodium Metabolism

The presence of salt and the maintenance of its retention constitute one of the most important factors in the storage of water and, therefore, the production of edema. The most significant feature of sodium metabolism relates to its retention. With an increased ingestion of sodium, the influence on edema production is, therefore, directly increased. We¹⁹ have shown in our patients

that the excessive intake of water alone is not injurious to the patient with pregnancy toxemia, provided reasonable investigation of the patient's status does not indicate an already overloaded circulation. However, if no consideration is paid to the presence of or the ingestion of sodium ion, then the introduction of large volumes of water into the organism results in retention of water and an increase in extracellular fluid. There is a direct proportion between body sodium content or sodium ingestion and edema, where fluid is continued to a point to permit the retention of isotonic sodium chloride. With low plasma protein concentrations, reabsorption of fluid in the tissues decreases.

FILTRATION FRACTION

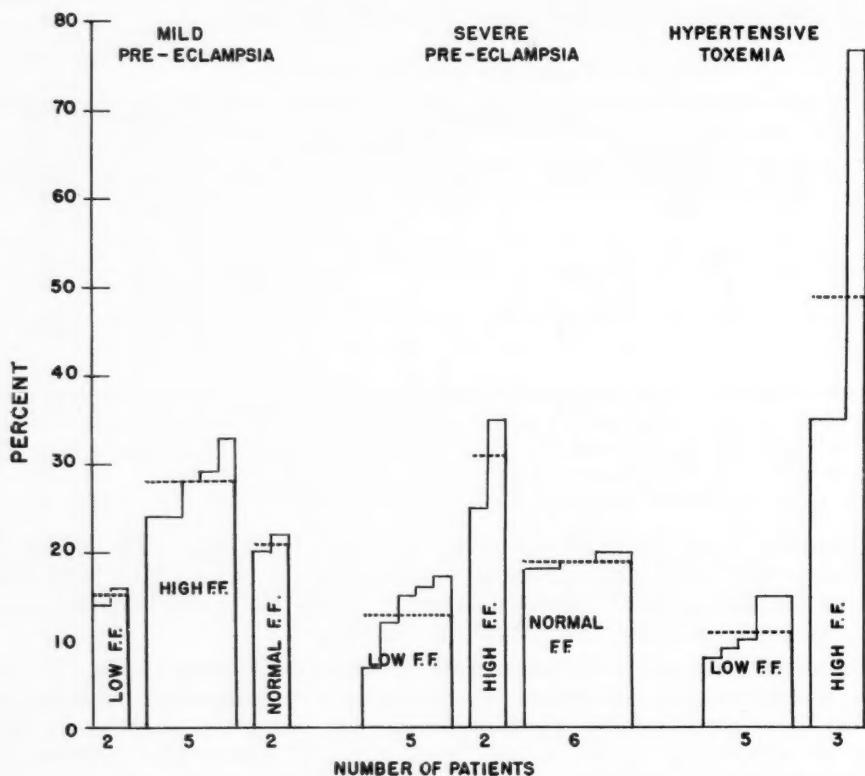


Fig. 6.

Water coming from the systemic circulation to dilute tissue fluids to isotonic levels is thus not readily removed. A decrease in plasma proteins, therefore, acts as the primary factor in the production of edema while the salt and water themselves play only a passive role, permitting more tissue fluid (isotonic) to be found.

Glomerular filtrate, on arrival at the end of the proximal tubule, is still in osmotic equilibrium with the plasma. Sodium and other urinary constituents are actively reabsorbed by the tubular cells and carry with them osmotically equivalent amounts of water. Since extracellular fluid contains 140 milliequivalents of sodium per liter, with every liter of edema formed, the individual goes into positive sodium balance by 140 milliequivalents if the sodium concentration of extracellular fluid is to remain normal. It thus becomes apparent that the body may lose its volume control but still maintains its con-

trol of tonicity. It has not yet been definitely proved that sodium is retained in excess of 140 milliequivalents per liter, although we know that it can be considerably lower. The utilization of extremely well-controlled sodium balance studies has much to offer in this regard.

In attempting to determine a relationship between glomerular filtration rates and sodium output (Fig. 8), we have always been led to believe that a very definite and direct relationship exists. In accepting the fact that glomerular filtration rate is reduced in the majority of patients with pregnancy toxemia, it may be safe to assume that sodium retention is due to more complete absorption by the tubules because of this allowed rate of filtration which would thus permit greater time for reabsorption. However, if this were so, we should

COMPARISON OF GLOMERULAR FILTRATION RATE TO
FILTRATION FRACTION

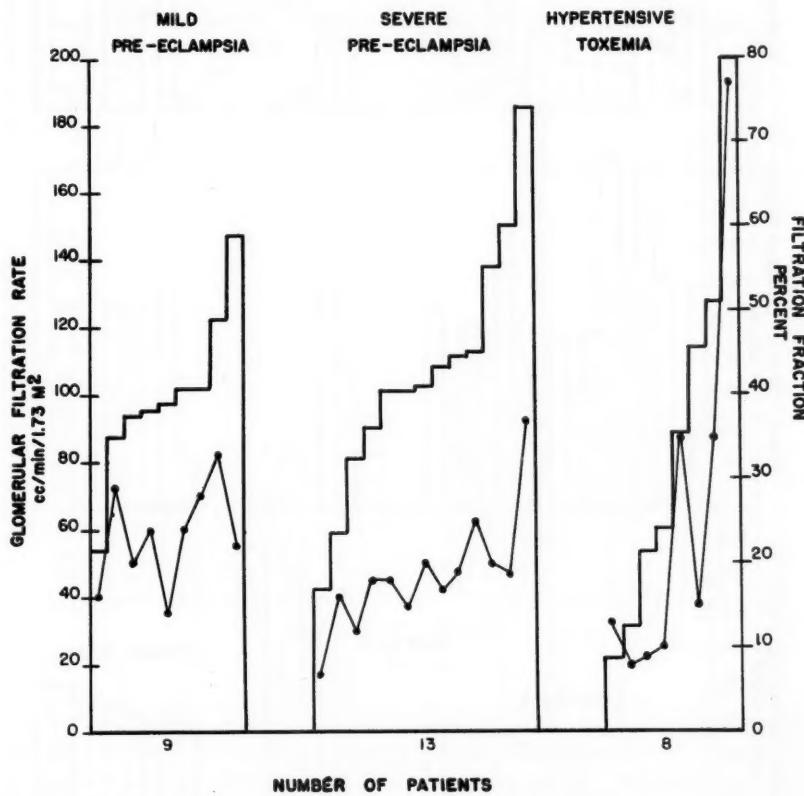


Fig. 7.

expect greater edema in patients with low filtration rates. Since glomerular filtration of sodium is proportional to the glomerular filtration rate of water, we expected changes that would bear out this established contention. We would, therefore, expect a constant relationship of decreased urinary sodium output to reduced glomerular filtration rate of water. This is certainly not so in our group of patients. However, among those with decreased glomerular filtration rates, there was a very definite increase in the concentration of urinary sodium and, where there was increased glomerular filtration rate, a very definite increase in urinary sodium concentration. This, we feel, is as it should be. In Fig. 9, in attempting to correlate glomerular filtration to urinary out-

put, a constant relation between changes in glomerular filtration rate and proportionate volumes of urine formation and excretion is not found; but, in some, the reverse is so. This may be explained as being due to a defect in tubular epithelium and may form the basis for the retention of water in some toxemias of pregnancy.

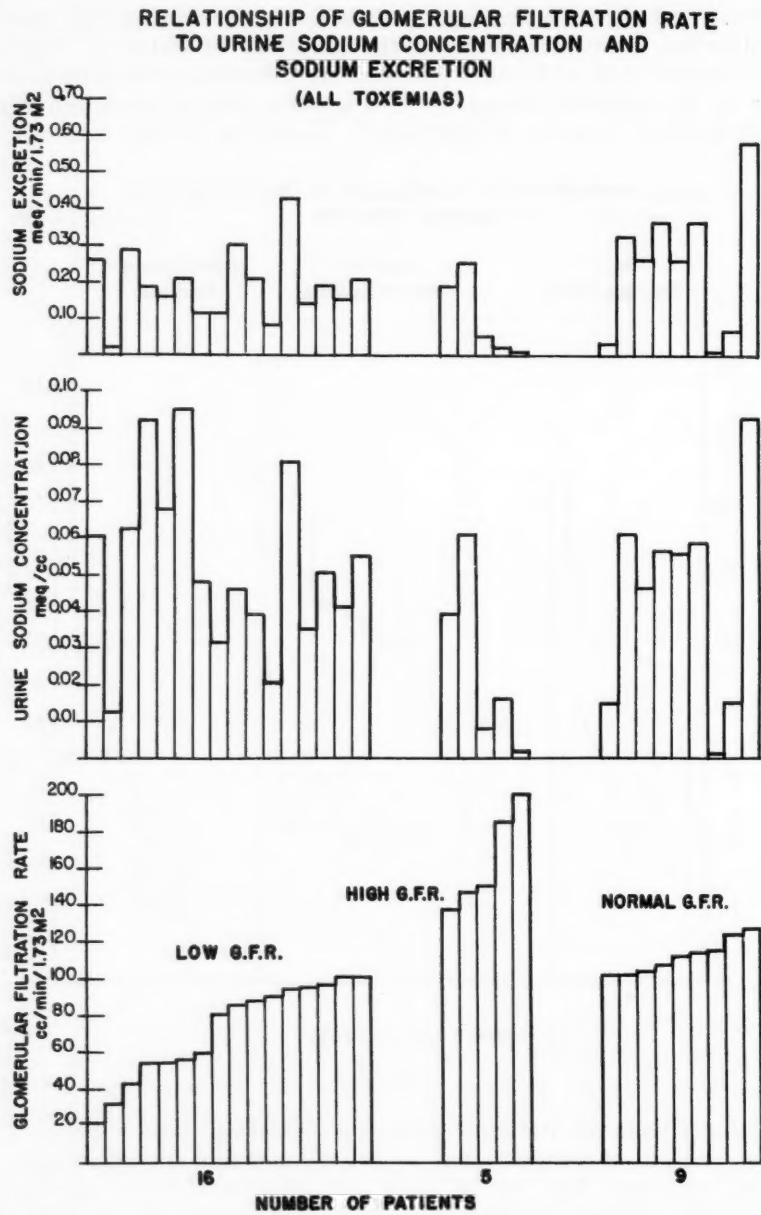


Fig. 8.

Taking this a step further (Fig. 10) and developing the relationship of urinary output to sodium excretion and the concentration of sodium in urine, we find, in any type of toxemia, that there exists no real correlation between the volume of urinary output and the excretion of sodium. The presence of

low sodium excretion and the presence of large urinary output has led us to believe that the presence of low plasma sodium represents an attempt by the body to conserve sodium and thereby prevent further loss of this ion. We likewise believe that the high excretion of sodium in our cases, usually where there is adequate urinary output, occurs as a result of an increased rejection fraction of sodium by the tubular epithelium as has been noted by Green and Farah.¹⁷

RELATIONSHIP OF GLOMERULAR FILTRATION
RATE TO URINE OUTPUT
(ALL TOXEMIAS)

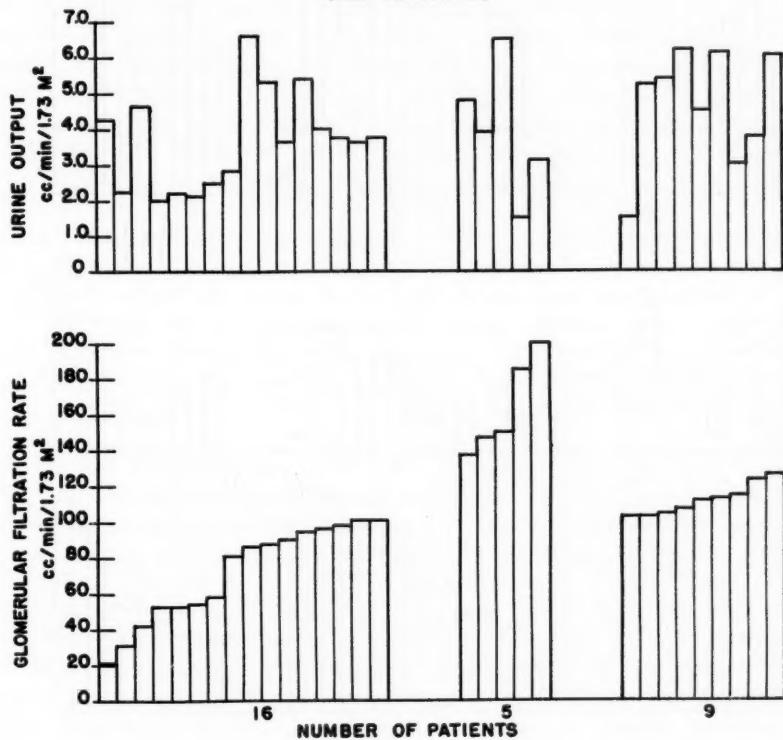


Fig. 9.

In our experience, we have found no constant relationship between water excretion and sodium excretion among our toxemic patients. In another study which is under way at the present time, a group of patients is being studied in whom the daily sodium intake is accurately known and the twenty-four-hour output of sodium is determined daily. On a measured low intake of sodium, resultant sodium excretion is found to be low. When these patients are on increased sodium intake, the rate of sodium excretion is also increased. We have also demonstrated that water diuresis is not dependent upon sodium diuresis and may occur in excess of sodium diuresis.

Comment

In the majority of our patients, as we have already noted, glomerular filtration rates were characteristically low or at the lower limits of normal. In pregnancy toxemia we feel that these occur on the basis of: (1) constriction of afferent glomerular arterioles, where there is an elevation of systemic blood

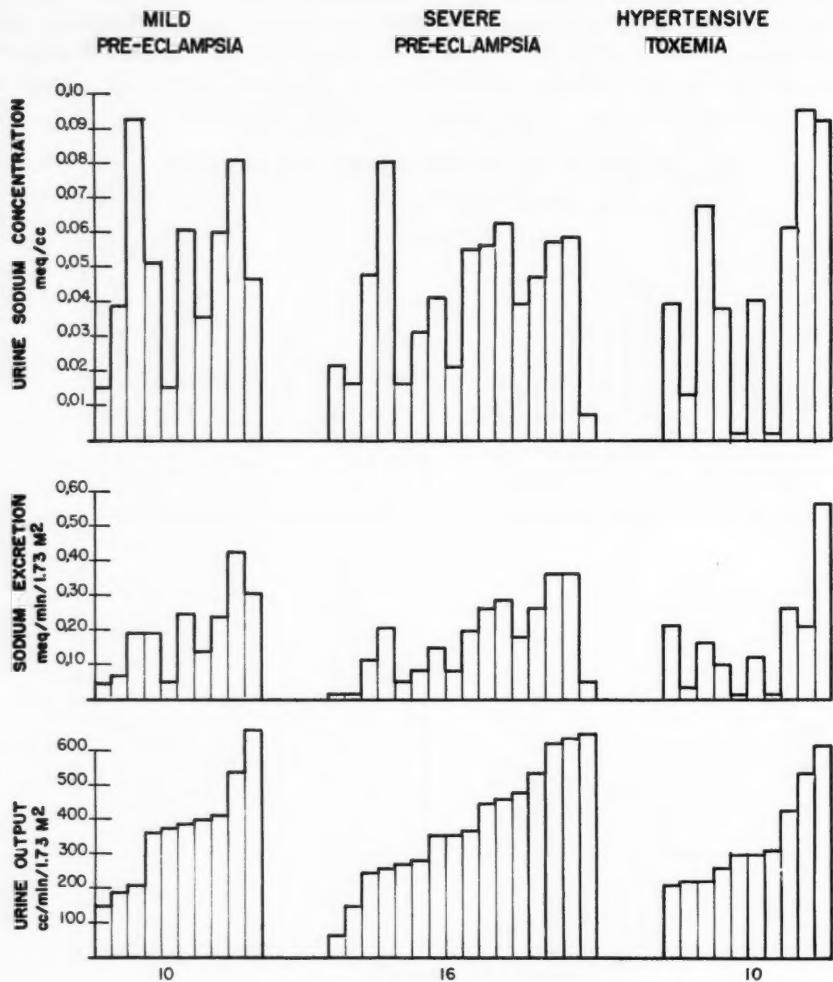
RELATIONSHIP OF URINE OUTPUT TO SODIUM EXCRETION
AND URINE SODIUM CONCENTRATION

Fig. 10.

pressure, (2) relaxation of the efferent glomerular arterioles, or (3) obstruction of the renal blood flow afferent to the glomerulus or capillaries (with its resultant fall in intraglomerular pressure). Where such obstruction to renal blood flow afferent to the glomerulus occurs, patients with toxemias of pregnancy present many of the same possible explanations for such happenings as are applied to other types of cardiovascular renal disease:

1. Decrease in the lumen of the interlobular arteries on much the same basis as decrease in the retinal vessels.
2. Decrease in the lumen of the afferent arterioles due to spastic (in specific toxemia of pregnancy) or sclerotic changes (in longstanding hypertensive disease).
3. Increased renal and capillary venous pressure such as occurs in the massively edematous individual.
4. Glomerular obliteration, with a possible explanation being based on flow through Trueta's¹⁸ shunt. In this group, I am considering those instances where a shunt of arterial blood may be the result of kidney edema.

Progressive decrease in glomerular filtration rate, or a sustained lowered glomerular filtration rate, in our patients would mean permanent disease; a return to normal would probably indicate the presence of spastic mechanisms. It is possible that all our pregnancy toxemias with reduced glomerular filtration rates could be attributed to peripheral circulatory failure, where relatively low blood pressure existed.

Glomerular filtration rates above normal levels would most likely be due to a constriction of the efferent arterioles with a concomitant decrease in the renal blood flow as a compensatory mechanism to maintain a high filtration fraction.

The occurrence of normal glomerular filtration rates, among our patients, is most logically based on the presence and maintenance of normal hydrostatic pressure levels in the glomerulus. Normal filtration rates in pregnancy toxemia also might well be considered as occurring in the presence of increased systemic pressure where efferent arteriolar tone in the glomerulus is also increased. Thus, with this rise in systemic blood pressure, the afferent arteriole constricts so that glomerular filtration rates, capillary pressure, and renal blood flow are maintained at the same normal levels. In a process presenting as many reversible features as are present in toxemias of pregnancy, these may be considered as compensatory mechanisms. Where a fall in systemic blood pressure has occurred, normal glomerular filtration rates occur with a dilatation of the afferent arteriole along with a simultaneous constriction of the efferent arteriole. Under these circumstances, renal plasma flow decreases but the capillary pressure rises sufficiently to maintain filtration rates within a normal range. Thus it can be seen that glomerular filtration rates within a normal range do not necessarily reflect normalcy in all mechanisms present in toxemias of pregnancy.

Where low renal plasma flows were found among our entire group of toxemic patients, constriction of efferent arterioles (on the basis of increased intra-glomerular pressure or added vascular resistance) forms the more plausible explanation. They could also be ascribed to increased filtration pressure or to obliteration of the glomerular bed. In addition to constriction of efferent arterioles, the other likely explanation would be the decrease in size of the lumina of blood vessels proximal to the glomeruli as occurs in sclerosis. In these instances of reduced renal plasma flow, where there is a distinct narrowing of glomerular capillaries before or during the toxemia, decreased glomerular filtration results. The filtration fraction would be nearly normal since there would be relatively little change in the intracapillary pressure.

In six patients with high renal plasma flows, we may state that some factor allowing marked dilatation of efferent glomerular arterioles is at work. The work of Trueta relates the possibility of shunts of blood supply around obliterated glomeruli so that the tubules have an independent blood supply. While this has been shown experimentally, its application to the human subject is still in the investigative phase but it may well explain some of the inconsistencies which we encounter in attempting to evaluate this problem.

Normal renal plasma flows in some patients could probably be described as being due to alterations in glomerular filtration as well as mechanics of efferent glomerular constriction acting in a compensatory fashion.

Therefore, on the basis of our data, it would seem that there is relatively little or no consistent relation between glomerular filtration rates, renal plasma flow, and sodium excretion in pregnancy toxemia. These data do, however, support a general reduction of glomerular filtration rate and the maintenance of normal filtration fraction in specific toxemia of pregnancy. However, a definite decrease in renal plasma flow and increase in filtration fraction are found among the hypertensive toxemia group. The excretion of urinary sodium seems to be influenced by the sodium intake and by the serum concentration.

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Discussion

DR. JOHN PARKS, Washington, D. C.—By a series of carefully conducted tests of renal function Dr. de Alvarez has focused our attention on the intricate physiology of the female kidney in pregnancy. To one interested, but incompletely initiated in the techniques of studying renal physiology, it might be thought that these results have been reported on a relatively small series of only 30 patients. However, when it is realized that each of these tests requires carefully controlled circumstances and time-consuming efforts, Dr. de Alvarez deserves high compliment on the volume of work which this study really represents. From a technical point of view, his use of a constant-speed infusion pump to maintain a continuous level of concentrations of the reagents used and his elimination of a possible added source of error by not using diuretics make this study all the more valuable.

Generalized and quite variable vasospasm is characteristic of pregnancy toxemia. The kidney is only one of the many vital organs involved. The essayist has suggested that the kidney may have some possible trigger mechanism responsible for the initiation of vasospasm. If this could be found and proved, the way would be open for a much clearer understanding of this disturbing disease so peculiar to pregnancy.

In his comparative study of glomerular filtration rate, renal plasma flow, filtration fraction, and sodium excretion, Dr. de Alvarez has reported on patients with mild pre-eclampsia, severe pre-eclampsia, and hypertensive toxemia. Concerning the controls, it is not entirely clear that they were normal pregnant patients evaluated under a similar method of study. Since it is a general impression that all physiologic functions are altered by eclampsia, it would be interesting to know if Dr. de Alvarez has had any experience with renal studies in patients just prior to or immediately following an eclamptic convolution.

Sodium retention is characteristic of developing pregnancy toxemia. The essayist has explained salt and water retention as secondary to lowered plasma proteins. The physiologic chemistry involved in the production of decreased plasma proteins and the possible retention of salt due to hormonal changes remain largely unsolved.

In his follow-up studies on these patients, particularly those with severe pre-eclampsia, it would be interesting to know how long it took to determine whether or not permanent renal damage resulted from the pregnancy toxemia.

Since the experimental tests reported today showed such wide individual variations, and since they are technically difficult to perform, it would seem that they have limited

value in clinical practice. It would be profitable to know what, in the author's experience, are the most practical methods of determining or predicting impaired renal function prior to the test of pregnancy itself.

Fundamental research of the type presented by Dr. de Alvarez should lead us closer to the solution of this problem of pregnancy toxemia.

DR. R. A. BARTHOLOMEW, Atlanta, Ga.—The literature dealing with toxemia of pregnancy has become exceedingly voluminous. When the problem of the etiology of toxemia is finally solved, it will be recognized that a great deal of what has been thought to be the cause has, in reality, been the effect.

I gain the impression from Dr. de Alvarez' paper that he regards the kidney as "the primary factor and initiator of the processes of toxemia of pregnancy." I believe that the weight of evidence indicates that the renal manifestations, both functional and pathological, are secondary and a part of the effect. The counterpart of a fulminating eclampsia is not to be found in renal disease *per se*.

The present-day trend of thought as to the etiology of toxemia of pregnancy as exemplified by Johnson and Page is that of a sequence of: (a) impaired blood supply to the uterus; (b) consequent ischemia of the entire placental area; (c) generalized villous necrosis; and (d) toxemia from absorption of breakdown products of chorionic degeneration.

Examination of formalin-fixed placentas from toxic patients indicates that it is not necessary to invoke a primary impairment of the maternal circulation to the placental area to explain villous necrosis. Gross and microscopic evidence indicates that the placental necrosis is localized and not generalized.

The primary circulatory disturbance apparently originates in obstruction to the return flow of fetal blood in one or more placental veins. The presence of muscular sphincters in these veins lends plausibility to this mechanism. The consequent distention of the villous capillaries causes enlargement and crowding of the villi. The intervillous spaces and intervillous maternal circulation become greatly diminished and villous necrosis ensues.

If this concept is true, based as it is on a consistent pathological picture, it follows that when true toxemia, either primary or superimposed, has reached a serious level, there should be no prolonged treatment purporting to correct a deranged kidney function; but rather there should be a prompt termination of the pregnancy to rid the mother of the placenta—the probable source of the poison.

DR. de ALVAREZ (Closing).—The question as to the most satisfactory means of evaluating the patient with pregnancy toxemia is a very difficult one to answer. As has been stated, no one determination is characteristic of pregnancy toxemia nor does any one laboratory procedure define the true state of renal damage. In our routine evaluation of the patient who has a toxemia of pregnancy or who is being evaluated following a previous toxemia in order that she may be advised regarding future pregnancies, we have found that the concentrating ability of the kidneys offers the most uniformly informative data regarding these patients' renal function. We have also found intravenous pyelography, where evidence of obstructive disease is found, to be the only other determination of practical significance. The urea clearance test, which is so commonly used in the evaluation of these patients, only gives us information as to the excretion ability of the kidney but gives no information of prognostic value.

The studies which we have outlined in this paper are of value from an investigative standpoint but cannot be used in routine evaluation.

We are familiar with the work of Dr. Bartholomew and his descriptions of the tissue pathology in the placenta. At the present time, we have perfusion experiments with placenta under way in an attempt to evaluate what is going on in the living placenta. We have found no constant relationship between the presence of infarcts in the placenta and the existence of severe toxemia of pregnancy. We hope that perhaps the physiologic and pharmacologic application to isolated placenta may give us similar results to those described in the tissue pathology by Dr. Bartholomew.

VAGINAL PLASTIC SURGERY IN THE TREATMENT OF LACERATIONS AND DISPLACEMENTS OF THE FEMALE GENITAL TRACT

A Study Based on 1,143 Patients Operated Upon From Jan. 1, 1938,
to Jan. 1, 1948*

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THE displacements of the genital tract are usually the result of childbirth. The few which occur as the result of trauma are seldom seen in the routine practice of gynecology. The history of the development of vaginal plastic surgery is an interesting one. Originally the technique consisted of simple denudation of the vaginal mucosa and approximation of the margins with sutures, while today the most careful dissection of the deep structures is carried out, and the tissues are approximated plane by plane. Two important factors in the plastic reconstructive surgery should be considered, first, adequate support without the loss of elasticity of the tissues, and second, the avoidance of atresia in any part of the uterovaginal tract.

In the displacements of the female pelvic organs five organs are involved. They may be affected singly or all five may take part in the lesion. The organs concerned are the urethra, urethrocele; the bladder, cystocele; the uterus, prolapse; the cul-de-sac of Douglas, posterior vaginal hernia or enterocele; and the rectum, rectocele. It is obvious from the foregoing that various techniques are necessary to correct the displacements of these organs, and that no one operation may be satisfactory in all grades and degrees of the same lesion. An operator may obtain considerable knowledge of what these reconstructions should be by examining a large number of women who have not borne children.

An analysis of my personal records for a period of ten years, namely from Jan. 1, 1938, to Jan. 1, 1948, shows that during that time I have performed vaginal plastic operations for genital displacements and lacerations on 1,143 women, and, since more than one procedure was employed in a large number of these women, it was determined that 2,176 separate operations were employed in the group. These procedures are listed in Table I.

*Read at the Seventy-Third Annual Meeting of the American Gynecological Society,
White Sulphur Springs, W. Va., May 11 to 13, 1950.

TABLE I. 1,143 VAGINAL PLASTIC OPERATIONS. LISTED PROCEDURES

	PRIMARY "A"	SECONDARY "B"
Vaginal Hysterectomy		
A. Lateral fixation of pedicles	86	3
B. Interposition of broad ligaments	67	
C. Clamp method	28	
D. Subtotal with interposition of cervical stump	6	
E. Composite, fundic	19	
Anterior vaginal hysterotomy	12	1
Manchester operation	96	
Interposition (Watkins, Schauta, Wertheim)	69	
High vaginal fixation of uterus	21	
Vaginal trachelectomy after supravaginal hysterectomy	19	2
Interposition of cervical stump	9	
Amputation of cervix	132	143
Bilateral trachelorrhaphy	133	11
Unilateral trachelorrhaphy	15	2
Anterior colporrhaphy	31	219
Plication of vesical sphincter	51	26
Operation for enterocele	32	19
Perineorrhaphy	141	614
Third degree perineorrhaphy	42	12
Plastic enlargement of vaginal orifice	27	
Colpocleisis	4	
Le Fort operation	9	
Vulvectomy	21	1
Operation upon vulvovaginal glands	10	5
Operation for urinary fistula	24	
Operation for rectovaginal and perineorectal fistula	6	8
Miscellaneous	33	
Totals	1,143	1,066

Column "A" lists the primary operations. Column "B" indicates that the listed procedure in "B" was performed secondarily to an operation included in "A." Therefore, the above-named procedures, excluding those under miscellaneous (33) were performed 2,176 times.

Vaginal hysterectomy in the treatment of prolapse of the uterus has greatly gained in popularity during the last two decades; indeed, it has replaced a number of the more conservative procedures. It is employed to its best advantage in the presence of a uterus that has undergone senile atrophy, in the presence of a hypertrophied uterus, and when there is the existence of concomitant disease. The greatest drawback of hysterectomy for prolapse is that, if recurrence takes place, the surgeon finds himself in the presence of an inverted vagina, a condition more difficult to cure than was the original prolapse. The principal advantage in conserving the uterus while operating for prolapse is that if recurrence does become evident, the surgeon still has the uterus to work with in order to overcome this operative complication.

Five methods of vaginal hysterectomy may be employed in the surgical management of uterine prolapse: A, vaginal hysterectomy with lateral fixation of the pedicles; B, vaginal hysterectomy with interposition of the broad ligaments, Mayo technique; C, vaginal hysterectomy, clamp method, Kennedy technique; D, subtotal vaginal hysterectomy with interposition of the cervical stump; E, composite operation (vaginal fundic hysterectomy, with or without amputation of the cervix and interposition of the remaining uterus). Each of these five methods has its application through the individualization of the patients.

Vaginal Hysterectomy With Lateral Fixation of the Pedicles.—

This is a very simple method of performing vaginal hysterectomy for prolapse, and is one that gives very good results. In my¹ experience, a posterior vaginal enterocele seldom occurs as a postoperative complication. In the performance of this type of operation, a circular incision is made around the cervix in the vaginal wall which is separated from the underlying tissues in all directions, the bladder and ureters are raised out of the way, the cul-de-sac of Douglas is opened, the first two fingers of the left hand are introduced posterior to the uterus, and the anterior peritoneal cul-de-sac is opened over the fingers. Starting on the left side, the uterosacral and cardinal ligaments are clamped together, cut, and ligated, the suture being held, and the uterine vessels are ligated separately. The same procedure is carried out on the right side. The fundus of the uterus is delivered through the anterior or posterior cul-de-sac of Douglas, whichever is easier, a clamp is placed close to the uterus on the left tube, ovarian ligament, and round ligament, and the tissues are cut between the clamp and the uterus. The middle portion of the broad ligament containing small vessels is clamped and cut. The two clamps are replaced by suture ligatures. There are three pedicles on each side; these are picked up on a suture of chromic catgut which is tied, the ends being left long. This process is then followed on the right side. The united pedicles are displaced laterally and the peritoneum is closed with interrupted sutures of fine chromic catgut, leaving a small opening through which a small Penrose tubing drain is inserted. The superior edge of the circular incision in the vagina is picked up with two Allis forceps. The anterior vaginal wall is separated from the bladder up to a point 1.5 to 2 cm. below the urinary meatus. The anterior vaginal wall is incised in the median line and two lateral vaginal flaps are developed and resected. There is left a wide triangular denudation, with the apex below the urinary meatus. The anterior vaginal wall is closed from above downward in one layer with interrupted sutures. The pedicles of each side, three in number, which have been previously threaded on a catgut suture, are attached by this suture to the extreme ends of the original transverse incision. These pedicles exert strong traction on the vaginal vault, which is then closed transversely with interrupted sutures, a small central opening being left for the exit of the drain. The perineum is then reconstructed.

In this group of patients under consideration vaginal hysterectomy with lateral fixation of the pedicles was performed 89 times; there were 86 primary and 3 secondary operations. In the 86 patients who had this procedure performed as a primary operation, the ages were: 20 to 29 years, 2 patients;

Fig. 1.—Vaginal hysterectomy with lateral fixation of pedicles.

- a. The uterus is extruded. A circular incision is made in the vaginal wall.
- b. The vaginal wall is separated from the uterus in all directions. A small opening is made in the cul-de-sac of Douglas with scissors, and the opening is enlarged with the fingers.
- c. The edge of the peritoneum of the cul-de-sac of Douglas is picked up with a fine catgut suture, the ends of which are held long.
- d. The bladder and the ureters are pushed upward away from the uterus, the anterior peritoneal cul-de-sac is opened and the edge of the peritoneum is picked up with a fine catgut suture, the ends of which are held long. The artist's drawing depicts the vagina, the bladder, and the peritoneum.
- e. The fundus of the uterus is delivered through the anterior or posterior cul-de-sac, whichever is more convenient. In this instance it has been delivered through the posterior cul-de-sac.
- f (lower). Because of the excessive length of the cervix, as downward traction was made on it, the fundus of the uterus appeared anteriorly, under the symphysis, and it was so held. The left broad ligament has been clamped in two sections. The lower section includes the uterosacral ligament, the cardinal ligament, and the vaginal and uterine vessels. The upper section includes the tube, the ovarian ligament, the round ligament, and the upper part of the broad ligament. It is occasionally necessary to use three clamps when the broad ligament is very wide. The clamps are being replaced by pulley sutures of chromic catgut. The right broad ligament is treated in the same manner.
- f (upper). Shows the method of applying the pulley sutures.

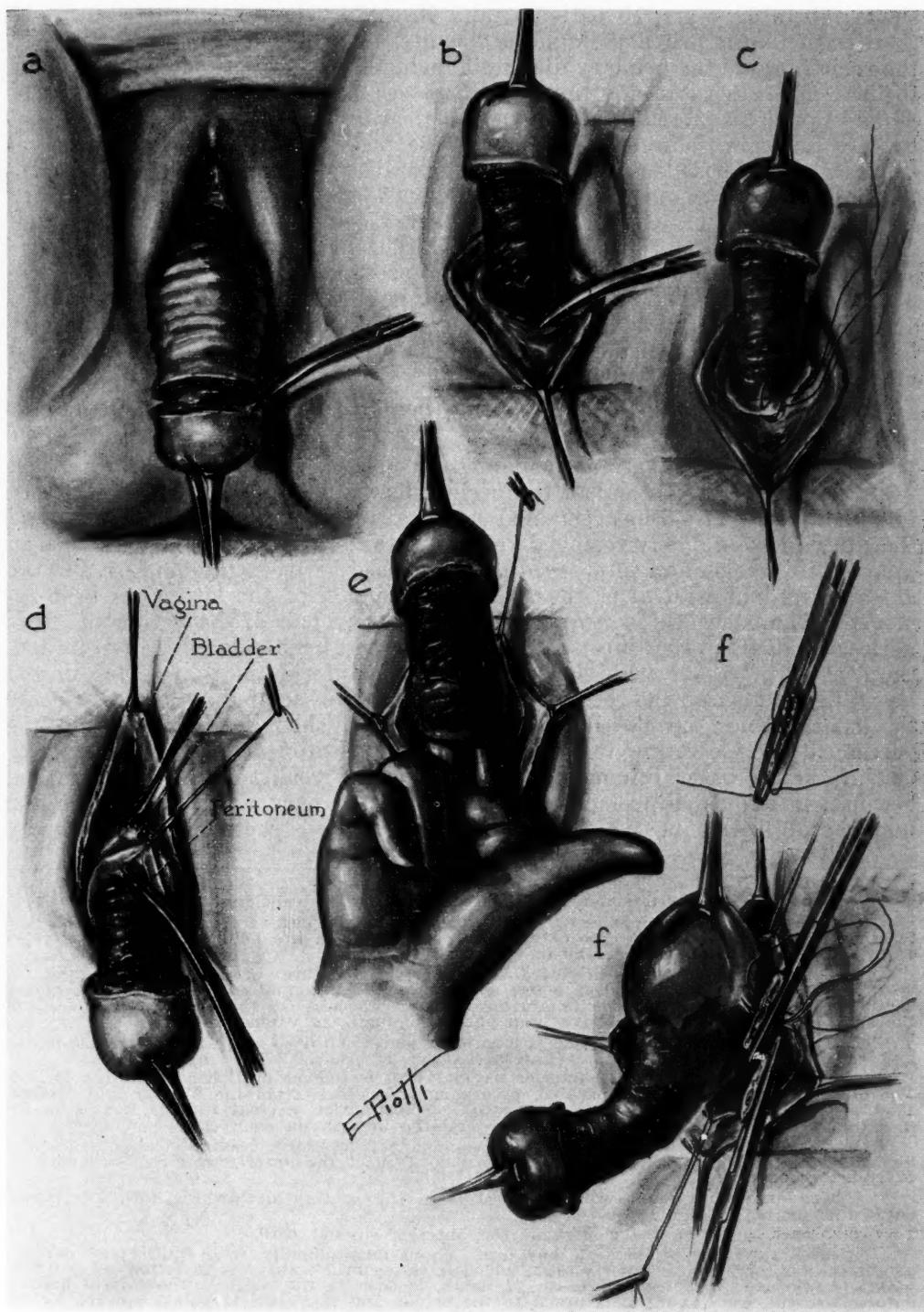


Fig. 1. (For legend, see opposite page.)

30 to 39 years, 2 patients; 40 to 49 years, 33 patients; 50 to 59 years, 22 patients; 60 to 69 years, 15 patients; and 70 to 79 years, 5 patients. In 57 of these patients the primary diagnosis was uterine prolapse, varying degree. In the remaining 29 the primary diagnosis included various lesions, too numerous to list. There were in addition 227 diagnoses of a gynecological nature, and 36 additional diagnoses of a nongynecological nature. Besides the 86 vaginal hysterectomies with lateral fixation of the pedicles, 140 concomitant operations were performed. Seven previous operations of a gynecological character and six previous operations of a nongynecological type had been performed on the 86 patients. General anesthesia was employed 39 times and spinal anesthesia 47 times. There was one death, 1.16 per cent, in the group, the result of coronary thrombosis, thirteen days postoperatively. There were three postoperative complications. One patient had partial intestinal obstruction, another pelvic cellulitis, and a third, phlebothrombosis with femoral vein ligation. All made satisfactory recoveries. Figs. 1 and 2 illustrate the technique of this operation.

Vaginal Hysterectomy With Interposition of Broad Ligaments (Mayo Technique).—

Vaginal hysterectomy accompanied by plastic repair of the anterior and posterior vaginal walls and of the perineum was first proposed by Charles H. Mayo, and his method has remained standard for many years. In this method the uterus is completely removed vaginally, the broad ligaments are joined in their entire length and interposed or transposed between the bladder and the anterior vaginal wall after the redundant portion of the latter has been removed. The operation is completed by a proper repair of the perineum. It is noticeable in this procedure that, after the broad ligaments have been united, there exists a rather wide space between the inferior margin of the united broad ligaments and the rectum. This is the cul-de-sac of Douglas. Obviously this space should be closed and this is accomplished by dissecting out the peritoneal sac, resecting this sac, closing the peritoneal edges and approximating the uterosacral ligaments. Herein lies the weak point of the operation, because, in extensive prolapse, which has existed over a period of years, the uterosacral ligaments, which at best are delicate structures, are markedly

Fig. 2.—Vaginal hysterectomy with lateral fixation of pedicles.

g. The uterus has been removed, the broad ligament pedicles of each side have been tied together with a suture of chromic catgut, the ends of which are held long. The peritoneal edges, above and below, are held by fine catgut sutures.

h. The peritoneum has been closed with interrupted sutures of fine chromic catgut. A small Penrose tubing drain, held by a fine silk suture at its vaginal end, drains the peritoneal cavity. The broad ligament pedicles are now extraperitoneal. On the right the two ends of the suture holding the pedicles have been passed through the vagina laterally.

i. The sutures holding the pedicles have been passed on each side of the vagina laterally and are in process of being tied. (Lateral fixation of pedicles.)

j. Traction is made on the anterior vaginal wall by means of Ochsner or Allis forceps. The anterior vaginal wall is separated, by means of scissors, from the bladder and urethra, to a point 1.5 cm. below the urinary meatus. The anterior vaginal wall is incised in the median line and dissected from the bladder and the urethra on each side.

k. The excess of the vaginal flap on each side is resected, leaving a wide triangular denuded area. The flap consists of the muscular layer of the anterior vaginal wall with its overlying mucosa.

l. The anterior vaginal wall is closed from the urethra downward, with interrupted sutures of chromic catgut.

m. Continuation of the closure of the anterior vaginal wall.

n. The anterior vaginal wall has been closed longitudinally with interrupted chromic catgut sutures to the transverse incision, which is closed in a transverse direction. The drain, which is removed at the end of 48 to 72 hours, is seen in the center. The lateral fixation sutures are cut, the vagina is returned to the pelvis, and the vault is pulled upward by the pedicles as soon as traction is released.

o. The perineum has been repaired in four layers, pubococcygei muscles, urogenital diaphragm, Colles' fascia, and skin. If an enterocele is present it is appropriately treated. The ends of the silk suture on the drain are held with a small strip of adhesive plaster. No knots are tied in the skin, the ends of the fine catgut suture are held with lead shots.

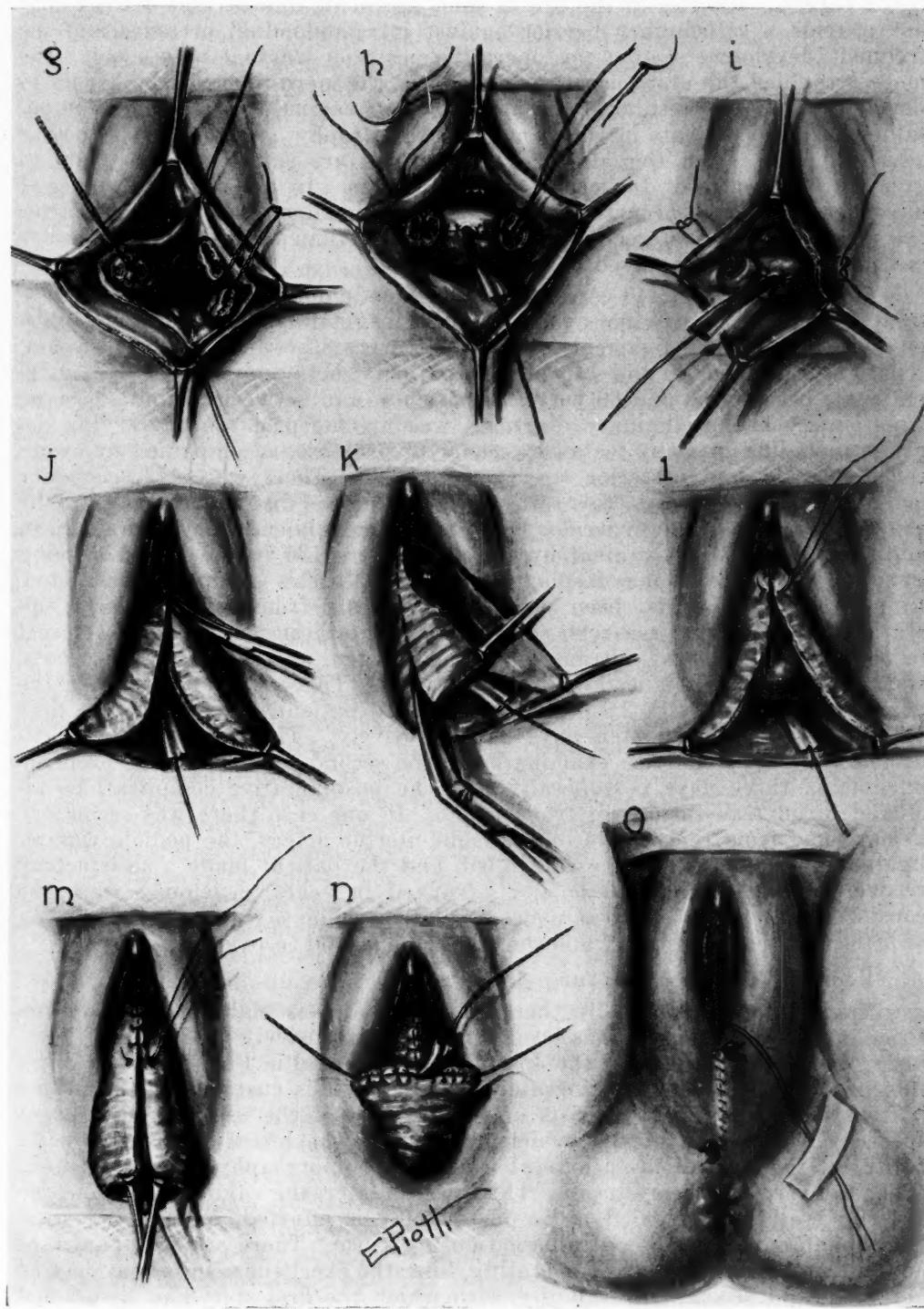


Fig. 2. (For legend, see opposite page.)

atrophied. I have demonstrated some that were no larger than a strand of No. 2 catgut. Manifestly the use of such ligaments and of such tissues does not provide a satisfactory barrier against intra-abdominal pressure and the frequent development of a postoperative posterior vaginal enterocele. The more atrophied the uterosacral ligaments are, the more likely is the hernia to develop. The good results of the Mayo type of vaginal hysterectomy are obtained in those patients in whom menopausal atrophy has not become too far advanced, and when the uterosacral ligaments are sufficiently adequate to give a firm closure of the cul-de-sac of Douglas. In my own experience, I have discovered the occurrence of a small or medium-sized enterocele after the Mayo vaginal hysterectomy more frequently than I have after any other method that I have employed.

In this study of 1,143 cases of vaginal plastic operations, 67 women were treated by the Mayo vaginal hysterectomy or vaginal hysterectomy with interposition of the broad ligaments. Their ages were: between 30 and 39 years, 2 patients; between 40 and 49 years, 16 patients; between 50 and 59 years, 20 patients; between 60 and 69 years, 22 patients; and between 70 and 79 years, 7 patients. The preliminary diagnosis was uterine prolapse of varying degrees, including in many instances recurrent prolapse, accompanied by cystocele, rectocele, and posterior vaginal enterocele. There were 177 secondary or additional diagnoses in this series of 67 cases; 163 diagnoses were of gynecological and 14 of nongynecological type. The supplementary operations in addition to the Mayo vaginal hysterectomy were 134 in number, 126 being gynecological and 8 nongynecological in type. In this group of 67 patients, 15 prior operations had been performed, ranging from vaginal plastic operations to a classical cesarean section. The anesthesia employed was spinal in 38 patients; general, nitrous oxide-gas, oxygen, and ether in 27 patients, and local infiltration anesthesia in 2 patients. There were 2 deaths in the group, or a mortality of 2.9 per cent. The first patient, 66 years of age, died of cerebral hemorrhage ten days postoperatively. This diagnosis was confirmed at the post-mortem examination. The second patient died of bronchopneumonia three days postoperatively. The postoperative complications included blood transfusions in two women: In one case there was secondary hemorrhage from the pedicle of the right uterine artery, the pedicle was re-ligated, the hemorrhage was controlled, and the patient made a satisfactory recovery. One woman, obese and advanced in years, developed what the consulting internist termed a neurocirculatory collapse; a blood transfusion of 500 c.c. was administered, and she also made a good recovery.

Vaginal Hysterectomy, Clamp Method.—

Vaginal hysterectomy by the clamp method was elaborated by Joseph Price of Philadelphia, and has been performed extensively by James W. Kennedy, who succeeded him at the Joseph Price Hospital in Philadelphia. When this procedure is employed for uterine prolapse it is customarily performed in two steps. The first consists of the removal of the uterus by means of specially constructed clamps which are left on the broad ligaments for 72 hours; at the same time an extensive anterior colporrhaphy is resorted to in order to overcome the cystocele. Three weeks later, the vaginal vault and the anterior wall being healed, a perineorrhaphy is effected, under local anesthesia, unless there is a contraindication to its use. There are two important advantages to this method of operating, first, the excellent results that may be obtained, and second, the rapidity with which the first step may be carried out, such a hysterectomy being performed in a few minutes. This is, therefore, an ideal method in the older group of women, and in those who are considered to be poor surgical risks. The principal disadvantage in this two-

stage operation is that it requires a longer stay in the hospital, but this actually may be considered an advantage in this group of patients, since it permits additional rest under close medical supervision and good nursing.

Twenty-eight women were operated upon by vaginal hysterectomy, clamp method. Their ages varied according to the following grouping: between 30 and 39 years, 1 patient; between 40 and 49 years, 2 patients; between 50 and 59 years, 7 patients; between 60 and 69 years, 13 patients; between 70 and 79 years, 4 patients; between 80 and 89 years, 1 patient. The primary diagnoses were severe laceration of the cervix with hypertrophy and ectropion in one patient; cervicitis with severe menorrhagia in another, and carcinoma of the cervix, Stage I (League of Nations), in a third. The remaining 25 patients had uterine prolapse in varying degrees. The secondary diagnoses for associated lesions were made for gynecological conditions in 40 and nongynecological conditions in 7, a total of 47 secondary conditions being observed in this group of 28 women. There were 22 concomitant operations of which 21 were gynecological and 1 nongynecological. Spinal anesthesia was used in 22 patients, general anesthesia in 3, and local infiltration anesthesia in 3. One of the patients in this group had had an interposition operation with amputation of the cervix and perineorrhaphy, and presented a recurrence after that operation. There was no mortality in this group of 28 women, 18 of whom were in the older age group, and most of them considered to be poor surgical risks. One postoperative complication occurred in the form of secondary hemorrhage from a vaginal slough. A vaginal pack and 500 c.c. of blood overcame this difficulty and she was discharged from the hospital in good condition.

Subtotal Vaginal Hysterectomy With Interposition of Cervical Stump.—

Six operations of this type were performed in this series of 1,143 patients. This method was chosen for those patients who had a good cervix, an enlarged corpus, who were bleeding excessively at the menstrual periods, in the absence of malignant disease in the uterus. The uterus was amputated at the isthmus or slightly above it and the cervical stump to which the ligaments of each side were attached was interposed between the bladder and vagina, and the intervention was completed by an anterior and posterior colporrhaphy and perineorrhaphy. The ages in this group were: between 30 and 39 years, 1 patient; between 40 and 49 years, 1 patient; between 50 and 59 years, 3 patients; between 60 and 69 years, 1 patient. The principal diagnosis was some degree of uterine prolapse, one having, in addition, a cystocele, and another a posterior vaginal enterocele. There were 17 supplementary gynecological and 1 nongynecological diagnoses; 14 additional gynecological operations were performed. Spinal anesthesia was used in 3 patients, and general anesthesia in 3. There was no mortality, and only one postoperative complication in the form of a small pulmonary embolus from which the patient promptly recovered.

Fundic Vaginal Hysterectomy, With or Without Amputation of the Cervix and Interposition of the Remaining Uterus.—

The cardinal ligaments, also known as the ligaments of Mackenrodt, and the parametria play an important role in the maintenance of the uterus at its proper station in the pelvis. Proof of this fact may be ascertained during the performance of an abdominal panhysterectomy. By placing a tenaculum on the uterine fundus and exerting traction upward, the uterus is not raised appreciably when the infundibulopelvic and round ligaments are severed, but almost always it can be raised to the abdominal incision, or close to it, when the cardinal ligaments are cut. Therefore, it is of great advantage to save the cardinal ligaments when operating for prolapse, if they are well developed and

not too attenuated. The above-named operation accomplishes this. A vaginal fundic hysterectomy is performed, the diseased cervix is amputated if necessary, the intermediate portion of the uterus, to which the cardinal ligaments are attached, is saved and interposed between the bladder and the vagina. In the early years of my practice I did the interposition operation frequently and resorted to this method when the uterus was too large to interpose because of myometrial hypertrophy and myomas, amputating the cervix or not, depending upon the presence or absence of disease in that organ. Spaulding employed this method also, but it was not until 1937, when Edward H. Richardson² presented it before the American Gynecological Society, that it became a definite entity in the management of prolapse. Since 1937 I have kept my operations of this type under a separate heading. In 1944, before the Section on Obstetrics and Gynecology of the American Medical Association, Te Linde presented the Johns Hopkins statistics on patients treated by this method. These statistics attested the fact that satisfactory and durable results may be obtained by this procedure, which Richardson described as "an efficient composite operation for uterine prolapse and associated pathology."

During the period of ten years under study, I have performed 19 of these composite operations. Between the ages of 30 and 39 years, there were 3 patients; between 40 and 49 years, 11 patients; between 50 and 59 years, 3 patients; and between 60 and 69 years, 2 patients. The main diagnoses were descensus uteri, 5 patients; first degree prolapse, 2 patients; second degree prolapse, 8 patients; and third degree prolapse, 4 patients. Sixty-five additional diagnoses were made, and 49 additional operations were performed, two of which were of a nongynecological character. Ten previous operations had been performed on these patients before they consulted me, these operations ranging from an Alexander suspension to vaginal plastics and abdominal fixation of the uterus. Nine patients had spinal anesthesia and ten general anesthesia in the form of nitrous oxide-oxygen and ether.

Anterior Vaginal Hysterotomy

This operation consists of incising the anterior vaginal wall transversely at the isthmus, separating the bladder and the attached vaginal wall upward, and incising the anterior lip of the cervix longitudinally to expose the pedicle of a pedunculated tumor or polyp. After excision of the pathological tissue, the cervical lip is sutured longitudinally and the vaginal wall transversely with fine catgut sutures. Twelve patients were operated on by this method, 4 for pedunculated myomas, 2 for cervical myomas, 5 for large cervical polyps, and 1 for multiple cervical polyps. The ages were: from 20 to 29 years, 1 patient; 30 to 39 years, 3 patients; 40 to 49 years, 2 patients; 50 to 59 years, 5 patients; 70 to 79 years, 1 patient. Additional gynecological diagnoses were made on 10 patients and additional nongynecological diagnoses on 3 patients. Nineteen additional gynecological operations were performed. General anesthesia was administered 7 times and spinal anesthesia 5 times.

Manchester Operation. Donald-Fothergill Procedure.—

The Manchester operation consists of uniting the cardinal ligaments (the parametria or bases of the broad ligaments) in front of the cervix, amputating the cervix when elongated, lacerated, or diseased, widely resecting the anterior vaginal wall and plicating the muscular coat of the vaginal wall which has remained attached to the bladder before suturing the anterior vaginal wall. A thorough repair of the pelvic floor or perineum is a complement of this operation. In 1903 Alexsandroff³ published a method of approximating the broad ligaments in front of the cervix when operating vaginally for uterine prolapse. Fothergill⁴ states, "The object of surgical intervention is to

shorten the pathologically elongated parametric tissues. They cannot be cut and absolutely shortened because they contain the blood-vessels, the lymphatics and the nerves of the uterus, but they can be relatively shortened by making them follow a longer course, namely by drawing them together in the middle line in front of the cervix. This manoeuvre pushes the cervix up and back into the hollow of the sacrum. It thus corrects retroversion, and this done, intra-abdominal pressure keeps the uterus in a position of anteversion. Recurrence of prolapse is thus prevented."

In 1915 I began to use this principle in an operation which I described in my records as the Alexsandroff principle, and which was added to other methods such as the interposition operation in certain cases. In 1933 Fletcher Shaw⁵ read a paper on the Manchester operation before the American Gynecological Society; this resulted in popularizing the method in America where it is now done extensively. This operation is especially useful in the presence of an atrophied uterus which the surgeon wishes to conserve, its performance is simple, and it is followed by good results.

In this series of cases the Manchester operation was performed on 96 women; their ages were as follows: between 20 and 29 years, 1 patient; between 30 and 39 years, 18 patients; between 40 and 49 years, 31 patients; between 50 and 59 years, 32 patients; between 60 and 69 years, 14 patients. The chief diagnoses were: desensus uteri, 29; uterine prolapse, first degree, 30; uterine prolapse, second degree, 20; uterine prolapse, third degree, 13; recurrent prolapse, first degree, 1; recurrent prolapse, second degree, 3. There were 312 additional gynecological diagnoses, which included 84 cystocele, 55 rectocele, and 75 lacerations and relaxations of the perineum, and 27 nongynecological diagnoses. In addition to the 96 Manchester operations 326 gynecological and 20 nongynecological operations were performed. Before admission to my service six of the patients in this group had had previous vaginal or combined operations for prolapse performed elsewhere. General anesthesia was administered 48 times, spinal anesthesia 43 times, and local anesthesia 5 times.

Interposition Operation (Watkins, Schauta, Wertheim).—

This operation, first performed by Thomas J. Watkins, of Chicago, in January, 1898, and published in 1899, has proved to be a valuable method of treating uterine prolapse when the indications laid down by its proponent are strictly followed. It is advised for first- and second-degree prolapse accompanied by a large cystocele. It is not intended for third-degree prolapse nor for the atrophied uterus. If it is employed at all in the presence of a small uterus, the uterine horns should be attached to the firm tissues covering the pubic rami as well as to the anterior vaginal wall. It was designed as an operative procedure to be used after the menopause. My former Chief, the late Dr. Frederick W. Johnson, began to do this operation at the Carney Hospital, Boston, in 1899, and it was he who taught me how to do it. A great number of these operations were performed in the Carney Hospital with satisfactory results. In 1943, I⁶ reported 224 personal operations, and, in 1946, my¹ series had reached 247 cases. The chief criticism over the years has been that this operation was followed by painful vesical disturbances. This distressful complication is inevitable if the fundus of the uterus is brought out between the bladder pillars and attached to the anterior vaginal wall, as I have seen it done. In cases so treated, cystoscopic examination will demonstrate that the bladder is sacculated and that its base is constantly pulled upon, resulting in pain on motion. Irritability of the bladder is rare, however, if the bladder is freely separated from its vaginal and uterine attachments, and its pillars are cut. The bladder thus becomes an abdominal organ, it rests on the superior and posterior surfaces of the uterus, and it lies smoothly, and not in

folds, over the interposed uterus. This may be easily demonstrated through a diagnostic cystoscope.

During the period of ten years under consideration in this study, 69 interposition operations were performed for the following diagnoses: descensus uteri, 4; first-degree uterine prolapse, 17; second-degree uterine prolapse, 16; third-degree uterine prolapse, 11; nulliparous prolapse, 2; second-degree cystocele, 4; third-degree cystocele, 15. There were 11 patients with third-degree prolapse upon whom this operation was performed. In each instance the uterus was of suitable or normal size, and had not undergone marked atrophy. In each instance the uterine horns were fixed to the firm tissues that cover the pubic rami and the anterior uterine wall was attached to the resected anterior vaginal wall in its whole length. All of the patients obtained durable results. Their ages were as follows: between 30 and 39 years, 1 patient; between 40 and 49 years, 5 patients; between 50 and 59 years, 31 patients; between 60 and 69 years, 27 patients; between 70 and 79 years, 5 patients. Additional diagnoses numbered 185. Of these 167 were of a gynecological and 18 of a nongynecological nature. A total of 203 supplementary operations were performed, 199 gynecological and 4 nongynecological. The uterus was curetted in all of the 69 patients, the perineum was repaired in 64, and the cervix was amputated in 23 and cauterized in 11. The uterine horns were fixed to the pubic rami in 19 of the cases. Spinal anesthesia was administered 48 times and general anesthesia 21 times. There was one serious complication, and this consisted of a postoperative phlebothrombosis; it was overcome by a bilateral femoral vein ligation and recovery resulted.

High Vaginal Fixation of the Uterus.—

This operation, which never obtained much popularity in America, has been done extensively in Germany and Austria, especially during the first three decades of this century. It is well illustrated in the important textbooks of these two countries. I have proved to my satisfaction that it is a valuable procedure, and with some modifications, I have found it especially so in recurrent uterine prolapse after fixation of the uterus to the anterior abdominal wall. In the performance of this type of operation, an incision is made in the anterior vaginal wall from a point below the urinary meatus to the cervix, two lateral flaps of the anterior vaginal wall are developed, the uterovesical ligament is cut, the bladder is separated from the uterus and raised under the symphysis, the peritoneal cavity is not opened. By traction on the cervix, the middle portion of the elongated uterus is exposed, three or four sutures of No. 1 chromic catgut are placed anteriorly on the uterus, at equal distances from each other, the ends are left long and held, and the sutures go through the peritoneum which covers the anterior surface of the uterus and through the uterus. The uppermost suture is placed at the level of the upper angle of the vaginal incision, the edges of the vaginal flaps are trimmed or resected, depending upon the amount of redundant tissue, the upper suture on the uterus is passed through the vaginal wall on each side and tied; this leaves the bladder above this suture, and overcomes the cystocele. The elongated cervix is amputated and reconstructed. The remaining sutures in the uterus are threaded through the anterior vaginal wall and tied, and the pelvic floor is repaired. Thus, the fundus of the uterus still remains attached to the anterior abdominal wall, the middle third of the uterus is faced to the anterior vaginal wall, the elongated cervix is amputated, and the perineum is reconstructed.

In this series high vaginal fixation of the uterus has been performed 21 times, and the ages of the patients were as follows: 30 to 39 years, 3 patients; 40 to 49 years, 7 patients; 50 to 59 years, 6 patients; 60 to 69 years, 5 patients.

The main diagnoses were: recurrent prolapse, first degree, 2; recurrent prolapse, second degree, 3; prolapse, first degree, 6; prolapse, second degree, 3; uterine descensus, 6; recurrent cystocele, 1. In addition there were 54 other gynecological diagnosis and 4 nongynecological diagnoses. In connection with these 21 high vaginal fixations of the uterus there were 77 additional operations, 76 being gynecological and 1 nongynecological in type. Ten of the patients had had previous operations for prolapse before consulting me, and one had had a prophylactic femoral vein ligation. General anesthesia was administered 8 times and spinal anesthesia 13 times.

Operations on the Cervix Uteri.—

Four hundred sixty-six operations were performed on the cervix uteri; these are tabulated as follows:

Vaginal trachelectomy subsequent to abdominal supra-	21
vaginal hysterectomy	
Interposition of cervical stump subsequent to abdominal	9
supravaginal hysterectomy	
Amputation of the cervix	275
Bilateral trachelorrhaphy	144
Unilateral trachelorrhaphy	17
 Total	 466

These operations on the cervix uteri were done, for the most part, as a step in general pelvic repair; they were seldom done alone. The ages of the 466 patients concerned varied between 30 and 79 years. There were two surgical complications in the form of secondary hemorrhages which occurred late in the convalescence when absorption of the catgut sutures began to take place. These hemorrhages were controlled by vaginal gauze tamponade and did not interfere with the recovery of the patients.

Anterior Colporrhaphy.—

Two hundred fifty anterior colporrhaphies were performed; 31 were primary and 219 secondary operations. The ages in the group of primary operations were: 20 to 29 years, 1; 30 to 39 years, 8; 40 to 49 years, 10; 50 to 59 years, 9; 60 to 69 years, 3. The principal diagnosis was: cystocele, first degree, 8; cystocele, second degree, 6; cystocele, third degree, 3; cystocele, degree undetermined, 5; recurrent cystocele, 7; urethrocele, 2. There were 58 additional gynecological diagnoses and 16 additional nongynecological diagnoses. Twenty of the 31 patients had had previous operations before they were referred to me, 15 being gynecological operations and 5 nongynecological operations. The concomitant operations were 78 in number and consisted of 73 gynecological and 5 nongynecological procedures. General anesthesia was administered 20 times and spinal anesthesia 11 times. There was one death in the group; this occurred on April 26, 1942, four days following anterior colporrhaphy, and was the result of cholecystitis and cholelithiasis.

Plication of Vesical Sphincter (for Stress Incontinence of Urine).—

A total of 77 plications of the vesical sphincter, of one form or another, were performed entirely through the vagina; 51 were primary and 26 secondary operations. The ages were: between 20 and 29 years, 2 patients; between 30 and 39 years, 10 patients; between 40 and 49 years, 21 patients; between 50 and 59 years, 14 patients; between 60 and 69 years, 3 patients; between 70 and 79 years, 1 patient.

In the 51 patients who had primary operations the principal diagnoses were relaxed vesical sphincter and stress incontinence of urine. There were 105 supplementary gynecological diagnoses and 18 supplementary nongynecological diagnoses. The main operation in 51 patients was the plication of

the vesical sphincter, and, in addition, there were 143 concomitant operations, 135 being of a gynecological nature and 8 of a nongynecological nature. In this group, 34 patients had had previous operations before consulting me, 30 gynecological and 4 nongynecological operations having been performed. General anesthesia was administered 32 times and spinal anesthesia 19 times. One complication was encountered; it consisted of a small pulmonary embolus. Bilateral femoral vein ligation was performed and the patient made a satisfactory recovery.

Operation for Posterior Vaginal Enterocoele.—

Posterior vaginal enterocoele was differentiated from a high rectocele and described as an entity by Marion of Paris, in 1909. He advocated the obliteration of the cul-de-sac of Douglas by means of superimposed pursestring sutures of nonabsorbable material, with the operation performed through the abdomen. In 1912 Moscheowitz of New York introduced a similar method in the treatment of prolapse of the rectum. This latter procedure could be used equally well in the management of posterior vaginal hernia. In 1922, George Gray Ward of New York proposed a vaginal operation for the radical cure of this hernia. His procedure, performed through the vagina, consists of mobilizing the cul-de-sac of Douglas on all sides, opening the hernial sac, reducing its contents, ligating its base, and resecting the sac. The uterosacral ligaments are united in their entire length by interrupted sutures as a protection against recurrence, and the perineum is repaired. Personally, I employ the Ward operation as routine and reserve the Marion and Moscheowitz procedures for extremely large hernias and those complicated by adhesions. In the period of years under study, namely from 1938 to 1948, I have performed 51 Ward vaginal operations for enterocoele, 32 of which were primary and 19 secondary. The ages of those in the primary operation group were: 30 to 39 years, 3 patients; 40 to 49 years, 7 patients; 50 to 59 years, 16 patients; 60 to 69 years, 5 patients; 70 to 79 years, 1 patient. The following primary diagnoses were made: enterocoele, 29; nulliparous enterocoele, 1; recurrent enterocoele, 2. The supplementary diagnoses were 22 gynecological and 5 nongynecological, a total of 27. The concomitant operations numbered 30; 27 were of a gynecological and 3 of a nongynecological type. Before consulting me, 29 of these 32 patients had had previous operations, 25 being gynecological and 4 nongynecological. General anesthesia was administered to 11 patients and spinal anesthesia to 21 patients.

Perineorrhaphy for Incomplete Lacerations of Perineum.—

Perineorrhaphy for incomplete lacerations of the perineum, or for a laceration that does not involve the sphincter of the anus, is one of the most common procedures employed in gynecology. It is performed relatively infrequently as a single operation; it is most usually done as the final step in an operation which consists of vaginal plastic repair. The technique of operation varies with different surgeons, but the fundamental principles remain the same. After the correction of the rectocele, the pubococcygeal portions of the levator ani muscles are united in the median line, the urogenital diaphragm, consisting of the transverse perineal muscles, deep and superficial, together with their investing fasciae, are approximated as a second layer; Colles' fascia is brought together as a third layer, and finally, the fourth layer, consisting of the skin, is united by means of fine interrupted sutures, or with a continuous suture. I have described a technique which has given me satisfactory results. From 1938 to 1948 I have performed 755 perineorrhaphies. Of these 141 were primary perineorrhaphies, and 614 were secondary or in connection with other operations. The ages of the 141 patients were: 20 to 29 years, 4 patients; 30 to 39 years, 31 patients; 40 to 49 years, 62 patients; 50

to 59 years, 34 patients; 60 to 69 years, 10 patients. The main diagnosis in the group of patients who had primary perineorrhaphies were: relaxed perineum, 67; lacerated perineum, 65; skin perineum, 3; scarred perineum with perineovaginal sinus, 3; dehiscence of perineorrhaphy, 1; perineovaginal sinus, 1. In the group 225 additional diagnoses of a gynecological nature and 66 of a nongynecological nature were made. There were 312 concomitant gynecological operations and 57 concomitant nongynecological operations performed. General anesthesia was administered 88 times, spinal anesthesia 43 times, local infiltration anesthesia, 9 times, and intravenous anesthesia once. There were 141 previous gynecological operations and 10 nongynecological operations. All perinei healed. I attribute whatever success I may have had with these operations to careful sharp dissection, complete hemostasis, free mobilization of the structures involved, approximation of the tissues without tension, layer by layer, with fine suture material, and meticulous nursing by nurses highly trained in this work.

Perineorrhaphy for Complete Laceration of the Perineum.—

Fifty-four women were operated upon for lacerations of the perineum which went through the sphincter ani muscle; 42 operations were primary and 12 secondary. Two types of procedure for this condition were employed, namely, the layer suture method, with rectal sutures, and the Warren flap method; the majority were operated upon by the first method. In the group of primary operations the ages were: between 20 and 29 years, 4 patients; between 30 and 39 years, 12 patients; between 40 and 49 years, 19 patients; between 50 and 59 years, 5 patients; and between 60 and 69 years, 2 patients. The principal diagnoses were: complete laceration of the perineum, one with rectovaginal fistula, 24; rectovaginal fistula, one multiple, 8; perineorectal fistula, one multiple, 5; laceration of rectum, 1; broken down third-degree repair, 1; improperly healed third-degree repair, 1; perineovaginal fistula, 1; markedly relaxed anal sphincter with incontinence, 1. There were 37 supplementary gynecological diagnoses and 2 supplementary nongynecological diagnoses. Thirty concomitant gynecological and 2 concomitant nongynecological operations were performed. Of these 42 patients, 35 had had previous operations before reporting to me; 29 had been of a gynecological nature and 6 of a nongynecological nature. Among these a previous perineorrhaphy for an incomplete laceration of the perineum had been performed on one patient; one previous operation for rectovaginal fistula had been performed on 2 patients; two previous operations for rectovaginal fistula had been performed on 7 patients. One woman had had 3 previous repairs and another 4 previous repairs. General anesthesia was administered to 27 patients and spinal anesthesia to 15 patients.

The results in 41 patients were entirely satisfactory. In one a second operation was necessary in order to obtain success. The following is a brief report of her case: This patient, a poorly developed and poorly nourished woman, had a complete tear of the perineum which had existed for years. She had had an abdominal pahysterection elsewhere, with a resulting large vesicovaginal fistula. An attempt was made to close this fistula, in another hospital, but this resulted in failure. When she consulted me her operation was performed in two stages. The vesicovaginal fistula was closed successfully through the vagina. After the fistula had healed, a second operation was performed, this for the repair of the complete tear of the perineum; the layer method and rectal sutures were used, and the skin was closed with prepared silk. The silk sutures were removed on the ninth postoperative day. Healing had not taken place and the tissues separated completely. She was taken to the operating room again, the edges of the wound were curetted and approximated in one layer with rustless steel alloy wire sutures. She

was given large doses of vitamin C. The perineum healed, and, when she was discharged from the hospital, she had continence of the bowel. Since that time several examinations have revealed satisfactory bladder and bowel control.

Plastic Enlargement of Vaginal Orifice.—

This plastic operation which is reserved for cases of apareunia, dyspareunia, and vaginismus in which conservative treatment, such as a dilatation of the vaginal introitus, has failed, was performed on 27 women. In this group the following ages were represented: between 20 and 29 years, 14 patients; between 30 and 39 years, 10 patients; between 40 and 49 years, 3 patients. The principal diagnoses were: apareunia, 15 patients; dyspareunia, 11 patients; vaginismus, 1 patient. There were 59 supplementary diagnoses of a gynecological nature and 5 of a nongynecological nature. Twenty-eight concomitant operations were performed, 22 gynecological and 6 nongynecological, while 5 previous operations, 2 gynecological and 3 nongynecological had been done.

Colpocleisis.—

Colpocleisis or the surgical closure of the vagina was carried out 4 times during the ten years under study, 1938 to 1948, on two women whose ages ranged between 40 and 49 years, and on two whose ages ranged between 50 and 59 years.

Three of these operations were performed for large vesicovaginal fistulas following panhysterectomy. In each instance the vagina was turned into an accessory bladder and urinary continence was restored. Two of these patients were very happy with the results that were obtained, and remained so during a long follow-up. The third patient, the youngest of the three, was strongly advised not to have the operation of colpocleisis performed, but to have ureterointestinal anastomosis; she categorically refused our advice and insisted on colpocleisis, even though it had been carefully explained to her that it would end her sex life. Colpocleisis was performed and she obtained urinary continence. Within two years she became dissatisfied and requested that the vagina be opened. Dr. Roger C. Graves, Chief of the Urological Department of the Carney Hospital, did the ureterointestinal anastomosis in two sessions. The vagina was then reopened, a dilating glass plug was worn at night for a number of months, and, when the patient was last seen she had a functioning vagina and urinary continence. The fact that she moved to California prevented further follow-up reports. The fourth patient in this group had had a Le Fort subtotal colpectomy, amputation of the cervix, and colpopерineorrhaphy. Recurrence took place in the form of prolapse of the bladder, vagina, and cul-de-sac of Douglas. Colpocleisis was performed, and the result was entirely satisfactory.

Three of four women in this group had had panhysterectomies and one a bilateral salpingo-oophorectomy before coming to me. As concomitant operations a Schuchardt incision and a suprapubic cystostomy were employed. In 3 patients healing took place by first intention, in one, the secondary suture of a small area in the line of closure had to be performed, and it was performed successfully. Three patients had spinal anesthesia and one general anesthesia.

Le Fort Operation. Subtotal Colpocleisis or Colpectomy.—

This procedure, which consists of the partial closure of the vagina, and which leaves a drainage canal running transversely below the cervix, with two canals running longitudinally, one at each side of the vagina to the vaginal orifice, has, and should have, a limited field of usefulness. The performance of this operation is restricted to the older women, to whom relief from a large protruding mass is more important than the continuance of the sex function, which, at best, is imperfect in women so afflicted. During the period under

discussion I have performed 9 of these operations. The ages were: between 50 and 59 years, 2; between 60 and 69 years, 3; between 70 and 79 years, 4 patients. The principle diagnoses were: inversion of the vagina following supravaginal hysterectomy, 4 patients; inversion of the vagina following clamp vaginal hysterectomy, 1 patient; inversion of the vagina associated with the procidentia of an atrophied uterus, 1 patient; uterine procidentia, one with a large enterocoele, 3 patients. The supplementary diagnoses were 13 gynecological and 1 nongynecological. There were 13 concomitant operations and 5 previous vaginal operations. Spinal anesthesia was administered 4 times and local infiltration anesthesia 5 times.

Vulvectomy.—

During the period under discussion, 1938 to 1948, vulvectomy was performed on 22 patients; primary vulvectomy on 21 and secondary partial vulvectomy on one. The ages of those who had primary vulvectomies were: between 40 and 49 years, 1 patient; between 50 and 59 years, 7 patients; between 60 and 69 years, 4 patients; between 70 and 79 years, 9 patients. The principal diagnoses were: carcinoma of the perineum, 1; carcinoma of the left labium minus, 1; atrophy of skin about the clitoris and the posterior commissure, 1; leucoplakia, 15, and kraurosis, 3. There were 16 supplementary diagnoses in the group, including kraurosis of the vulva, kraurosis of the vulva and anus, cervical polyp and myomas. In addition there were 3 supplementary diagnoses of a nongynecological nature. Nine concomitant operations were performed, 8 gynecological and 1 nongynecological. Spinal anesthesia was administered to 13, general anesthesia to 7, and local anesthesia to 1. One complication occurred. It consisted of phlebothrombosis, on the second postoperative day; it was overcome successfully by femoral vein ligation.

Operations on the Vulvovaginal Glands.—

Ten operations were performed on the vulvovaginal glands; they consisted of: excision of one gland in 6; excision of two glands in 1, and incision and drainage of one gland in 3. The ages were: 20 to 29 years, 4 patients; 30 to 39 years, 3 patients; 40 to 49 years, 2 patients; 50 to 59 years, 1 patient. The principal diagnoses were: unilateral vulvovaginal cyst, 6; bilateral vulvovaginal cyst, 1; abscess of vulvovaginal gland, 1; infected hemorrhagic cyst, 1, and hemorrhagic cyst, 1. There were two supplementary gynecological diagnoses, metrorrhagia and erosion of the cervix, and two concomitant operations were performed. General anesthesia was administered to 8 patients, and spinal anesthesia to 2. The only complication was the formation of a hematoma, which was drained, and which healed satisfactorily.

Operation for Urinary Fistula.—

Twenty-four operations for this condition were carried out, 20 for vesicovaginal fistula and 4 for urethrovaginal fistula with the supplementary diagnosis of laceration of the cervix made twice. The ages were: 20 to 29 years, 1 patient; 30 to 39 years, 6 patients; 40 to 49 years, 12 patients; 50 to 59 years, 3 patients; 60 to 69 years, 2 patients. The causative factor of the fistulas in these 24 patients was: abdominal panhysterectomy, 6; anterior colporrhaphy, 2; Manchester operation, 1; plication of vesical sphincter, 1; amputation of cervix, 1; difficult deliveries, 13. The previous attempts at closure of the fistulas were: one previous attempt in 5 patients; two previous attempts in 2 patients; three previous attempts in 1 patient; four previous attempts in 1 patient; six previous attempts in 1 patient; not previously attempted in 14 patients. As concomitant operative procedures 9 suprapubic cystostomies were performed for constant urinary drainage on 9 patients who had had

closure of the fistula through the vagina. Spinal anesthesia was administered to 8 and general anesthesia to 16. The complications consisted of 4 recurrences. In one the recurrent small fistula healed spontaneously, in two a second repair operation was successful, and in the fourth the ureter was transplanted into the bladder, with resulting satisfactory function.

Operation for Rectovaginal and Perineovaginal Fistula.—

The cases of 14 women are included in this group. There were 6 primary and 8 secondary operations. The ages were: 30 to 39 years, 3 patients; 40 to 49 years, 2 patients; 50 to 59 years, 1 patient. The principal diagnoses in the 6 primary cases were: perineorectal fistula, after 3 previous repairs of a complete laceration of the perineum, 1; perineorectal fistula after excision of vaginal cyst, 1; perineorectal fistula, 1; large rectovaginal fistula, 1; high rectovaginal fistula after repair of complete laceration of the perineum, 1; rectovaginal fistula and complete laceration of the perineum after vaginal hysterectomy and four operations on the perineum, 1. The supplementary diagnoses were 5 gynecological and 1 nongynecological. The concomitant operations numbered 7, all of which were gynecological in nature. Before these patients were referred to me, 7 previous operations had been performed. The anesthesia consisted of general anesthesia in 4 and spinal anesthesia in 2. There were no complications in the group.

Miscellaneous Operations.—

In reviewing the vaginal operations performed during this ten-year period, 1938 to 1948, 33 women were placed in the miscellaneous group. Their operations consisted of the following: resection of a vaginal scar, dilatation of the vagina, and insertion of a glass vaginal plug, 1; formation of an artificial vagina, Wharton technique, 3; resection of redundant mucosa at introitus after Wharton operation, 1; resection of hymenal tab, 3; vaginal plastic operation to reopen vagina closed by colpocleisis, 1; excision of condylomata acuminata, 1; resection of vaginal septum with insertion of glass plug, 2; excision of urethral caruncle and cauterization of base, 1; excision of redundant urethral mucosa, 2; excision of vaginal cyst, 2; excision of polyp of anterior vaginal wall, 1; excision of endometriotic nodules of vagina and cervix, 1; resection of vaginal vault for recurrent adenocanthoma followed by 3,000 mg. hr. radium, 1; reduction of bladder through vaginal vault, with closure of vault, 1; vaginal excision of prolapsed tube following vaginal hysterectomy, 1; resection of tumors of rectovaginal septum, 2; resection of labia minora, 1; excision of sebaceous cyst of labium minus, 5; excision of papilloma of labium minus, 1; excision of perineal cyst, 2.

In the 33 miscellaneous operations the ages were: between 20 and 29 years, 8 patients; between 30 and 39 years, 12 patients; between 40 and 49 years, 6 patients; between 50 and 59 years, 3 patients; between 60 and 69 years, 3 patients; between 70 and 79 years, 1 patient. The 33 main diagnoses corresponded with the 33 operations listed. There were 24 supplementary diagnoses; 15 concomitant operations were performed, and 11 patients in the group had had previous operations before consulting me. General anesthesia was administered to 18 patients, local anesthesia to 4, and intravenous anesthesia to 11.

Mortality

In the group of 1,143 patients who were operated upon vaginally during the period under discussion, 1938 to 1948, 186, or 16.2 per cent, were over 60 years of age. There were four deaths, a gross mortality of 0.34 per cent. The causes of death were coronary thrombosis, thirteen days after vaginal hysterectomy with lateral fixation of the pedicles; cerebral hemorrhage, ten days after vaginal hysterectomy with interposition of the broad ligaments; broncho-

pneumonia, three days after vaginal hysterectomy with interposition of the broad ligaments; biliary disease, cholecystitis and cholelithiasis, four days after anterior colporrhaphy.

Results

The prime purpose of this paper is to discuss the various operative methods that were employed in the treatment of 1,143 women who had displacements and lacerations of the genital tract, by means of 2,176 procedures. In such a study the question of postoperative recurrence must be given due consideration. There are three definite factors of prime importance in so far as the results following vaginal plastic operations are concerned; namely, the age and general condition of the patient, the condition of the tissues that must be brought together for support, and the type of work that the patient expects to do following operation. The same operative procedure employed for the correction of lacerations or vaginal displacements obviously should give a better result in a patient 45 years of age than in one 75 years of age. Under ideal conditions a recurrence rate of about 5 per cent should be expected, although in some series of my cases it ranged between 8 and 10 per cent. The rate increases as the years elapse following operations, because of the natural atrophy of the tissues. The recurrence may take the form of a cystocele, rectocele, enterocele, and uterine prolapse of varying degrees. Rarely a combination of all four may be present. In my experience these recurrences may be improved upon by a secondary operation, which has been performed on many of my patients.

The results of vaginal plastic surgery depend, to a great extent, on individualizing the patient and choosing the best method for the particular condition, rather than to attempt to adapt a particular method to all cases.

Summary and Conclusions

A study based on 2,176 procedures in vaginal plastic surgery, performed on 1,143 women during a period of ten years, is presented.

No single method or operation for a given condition is applicable to all cases. The best results may be obtained by selecting the best procedure for a given case.

In this group of 1,143 women, 16.2 per cent of whom were over 60 years of age, there were four deaths, an uncorrected mortality of 0.34 per cent. The causes of death were coronary thrombosis, cerebral hemorrhage, bronchopneumonia, and biliary disease.

Twenty-seven different procedures were employed, and each is briefly discussed. All types of anesthesia were used; local and spinal anesthesia offer many advantages in vaginal plastic surgery.

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Discussion

DR. LAWRENCE WHARTON, Baltimore, Md.—I think Dr. Phaneuf has stressed from the beginning one of the basic principles of plastic surgery, a principle that was taught to his house staff by Howard Kelly, that each case is a problem by itself. The basic anatomic factors that produce prolapse vary in different patients and the surgeon who does a good job discovers those and corrects them individually. I would go farther than Dr. Phaneuf has gone in this listing of considerations and indications. I would even say that no one can tell exactly what he should do—what type of operation is best adapted to the case—until the patient is examined under anesthesia, and sometimes in the course of operation one may have to change one's entire procedure. Curettage, that is routinely done in the Manchester operation, may reveal something that is suspicious so, instead of doing a Manchester, it may be necessary to do a vaginal hysterectomy. I do not think one should ever approach the problem of prolapse with fixation in mind.

Dr. Phaneuf's choice of operations agrees substantially with mine, so I have no quarrel with him there. The one particular in which I would differ with him is operative procedures. I was brought up under the technique of Dr. Kelly and used the interposition operation a great deal. I have slipped backward in that. I am reneging because I do not believe the interposition operation offers the advantages some others do. I think the Manchester operation will do as good a job, or better, than the interposition in most cases. Fundamentally, I feel the most important reason for my having ceased to do the interposition operation is not because of the failure to get a good result but in a few cases that I have seen I have had to do total hysterectomy for carcinoma of the endometrium in patients who have had interposition operations and the procedure is extremely difficult. It often involves injury to the bladder and I do not believe it is fair to subject any woman to that hazard in her future life if there is another operation that will give her the same benefits. I have not done many interposition operations recently.

The type of vaginal hysterectomy used varies with the clinic. Every person has his own method. Dr. Phaneuf stressed and described the type in which the broad ligament and the round ligament are brought together and interposed under the bladder and sutured to the suprapubic arch. I like that procedure. I believe that, using that procedure, you could guarantee the patient not to have trouble with cystocele. Dr. Phaneuf had more time to go into this procedure in detail in his manuscript for publication than he could present this morning, but in that operation he suggested that the fixation of the broad ligament under the pubic arch left behind an open space, the cul-de-sac of Douglas, which might develop a hernia.

The other operations which he discussed are used generally, as he indicated, and we all get fairly good results with them. While the techniques are uniform there are certain failures and I think to these failures we should give more attention.

Failure in these cases may be due to many things. In my own experience in the Manchester operation when I did not remove the cervix I have occasionally failed. The cervix looks quite normal sometimes and you are tempted to leave it in, and I think this temptation to leave the cervix in invites trouble later on. I do not believe you can bring the broad ligaments together without high amputation and, if you do that, you can almost guarantee the woman that she will not have trouble again of that sort.

Failure may also be due to failure of healing of the tissues or due to infection. Dr. Phaneuf mentioned the cul-de-sac of Douglas as the site of failure after the Mayo hysterectomy. I would like with his permission to enlarge that statement and include not only those that follow a Mayo type but all operations for prolapse. Practically all failures I have seen in my own and other cases have been due to some fault in the cul-de-sac. It is a hernia and I do not know of any type of hernia in which there is 100 per cent cure; so we are bound to have failures where there is not much tissue to work with. In my experience I have found the best way to avoid postoperative hernia of the cul-de-sac of Douglas is to dissect up the posterior vaginal wall to the cervix and dissect out all loose

tissues; correct the hernia, ligate it high and bring the ligaments together, approximate the vaginal wall, and close off or obliterate the cul-de-sac. Notwithstanding this, I have had some failures and enteroceles may recur.

DR. PHANEUF (Closing).—It is true that we change our procedures from time to time, in the treatment of uterine prolapse and like Dr. Wharton I have done fewer interposition operations in recent years. I have not given it up entirely because I find that with a prolapse of the uterus which does not come down any farther than a second degree, i.e., extrusion of the cervix uteri, with a large cystocele, in older women, the interposition operation is an ideal procedure. I agree with Dr. Wharton that the performance of a total hysterectomy for a carcinoma of the endometrium after this procedure is difficult, yet, in those that I have done, the intervention was completed without any injury to the bladder. If one does this operation on elderly women and if the uterus has been curetted and is free from carcinoma, the percentage of patients developing carcinoma of the endometrium is small. However, this does not change the point made by Dr. Wharton that hysterectomy following the interposition operation is difficult.

Methods of doing vaginal hysterectomy differ with different operators. The reason I have changed from the Mayo technique is because after the union of the broad ligaments in the median line and their interposition between the bladder and the vagina, there remains a wide space between the inferior margin of the united broad ligaments and the rectum, the cul-de-sac of Douglas. An attempt is made to close this space by uniting the uterosacral ligaments which, at best, are attenuated structures. This weak spot accounts for the high percentage of enteroceles following this type of operation. For a number of years I have fixed the broad ligament pedicles to the lateral edges of the vagina in the performance of vaginal hysterectomy, in reality an abdominal panhysterectomy, in reverse. I have improved my results considerably by so doing. I have had a follow-up of these cases and thus far I have found but one enterocele and this was corrected by a second operation.

The point made by Dr. Wharton of the removal of the cervix in the Manchester operation is excellent. I do it in almost all cases because I reserve this type of operation for patients who have passed the childbearing age. In them, the removal of the cervix is of no future importance since it cannot complicate subsequent childbirths.

CHANGING INDICATIONS FOR HYSTERECTOMY IN THE CLIMACTERIC WOMAN*

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THE development of a satisfactory therapeutic regimen for correction of any physical abnormality depends not only upon its effectiveness but upon the safety with which it may be employed. Compromises in selection of treatment may become necessary if one method, in some respects less desirable than another, offers a solution while exposing the patient to a substantially lower risk. This becomes of particular importance in the management of benign conditions which may be in themselves less lethal than the therapy designed to correct them. The belief of one of us^{1, 2} that the production of irradiation menopause was the preferable method for controlling most cases of benign climacteric uterine bleeding was based primarily upon the fact that the mortality associated with any type of hysterectomy was far higher than that following irradiation and possibly even higher than the potential deaths from malignancy which might develop in the retained uterus. As more and more such irradiated patients were observed and compared with others who because of contraindications to castration had been managed by hysterectomy, it became apparent that those in the latter group were by and large in better physical and mental condition than the former. In addition the presence of the uterus made frequent examinations mandatory, as well as, in those who at any time after irradiation developed an abnormal discharge from the vagina, hospitalization for diagnostic dilatation and curettage. In the absence of the cervix and uterus discharge from lesions such as atropic vaginitis was less of a diagnostic and therapeutic problem since uterine malignancy as a cause was impossible. We have noted in our own practice a trend away from irradiation for the control of abnormal bleeding in these women and in order to evaluate the results of this change the records of the patients presented here were analyzed.

Material and Results

From Jan. 1, 1947, until Jan. 1, 1950, 753 hysterectomies for benign pelvic conditions were performed on the ward and private services of the Department of Obstetrics and Gynecology of the Temple University Hospital. Of these 360 were done on the ward service primarily by the resident staff under the supervision of the attending staff of trained obstetricians and gynecologists who in turn performed 393 operations on the private patients. Of all the operations 606 (80.5 per cent) were total abdominal, 45 (6 per cent) were subtotal ab-

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dominal, and 102 (13.5 per cent) were vaginal hysterectomies. The only death in the entire series occurred in a private patient who was operated upon to control bleeding from uterine leiomyomas complicated by extensive chronic pelvic inflammatory disease and who died of peritonitis from a small unrecognized perforation of the rectum. The mortality rate for the operation for benign disease during the three-year period is therefore 0.13 per cent.

From the entire group of hysterectomies the records of the 271 patients between the ages of 40 to 55 years were analyzed more thoroughly and the figures to be reported here are based only on these. One hundred thirty-seven, or 50.5 per cent, of these women had either relaxation of pelvic supporting structures which could not have been corrected by castration or bleeding associated with pelvic abnormalities which contraindicated irradiation and therefore were not suitable candidates for treatment other than removal of the uterus (Table I). Only 54 of these were private patients and 69 white; almost all the vaginal hysterectomies done primarily for prolapse were in this group. The lesions in the remainder were characteristic of those regularly encountered on award service made up predominately of Negro patients. The size of the uterus varied from that comparable to a 12 to 14 weeks' gestation to those which filled the entire abdominal cavity; pain, pressure, and degeneration of the fibroids were common. In many a history of recurrent attacks of pelvic infection was obtained and examination revealed changes compatible with chronic quiescent tuboovarian disease. Total abdominal hysterectomy was performed in 102 (74.6 per cent), subtotal abdominal hysterectomy in 7 (5 per cent), and vaginal hysterectomy usually associated with vaginal plastic in 28 (20.4 per cent). Thirty-seven (27 per cent) of the patients experienced a morbid postoperative course (Table II) and the one death in the series occurred in this group.

TABLE I. LESIONS CONTRAINdicATING CASTRATION. DIAGNOSES

Leiomyomas	
Uncomplicated	49
With tuboovarian disease	25
With pain or pressure	22
Pelvic relaxation	29
Endometriosis	10
Tuberculosis	1
Ovarian neoplasm	1

TABLE II. LESIONS CONTRAINdicATING CASTRATION. POSTOPERATIVE COMPLICATIONS

Urinary tract infection	12
Vaginal cuff infection	8
Pelvic cellulitis	4
Atelectasis	3
Wound infection	2
Wound bleeding	2
Thrombophlebitis	2
Pneumonitis	1
Ureteral injury	1
Peritonitis (death)	1
Unknown cause	1

In the remaining 134 the important problem was uterine bleeding since in each instance the patient was admitted to the hospital for investigation and control of prolonged or irregularly spaced periods. The amount of flow and the duration of the deviation from the normal pattern were variable but in each instance it was the opinion of the physician in charge that control of

bleeding in addition to accurate diagnosis was necessary. In contrast to the other group, almost all these patients were white women and private patients who sought medical advice before their lesions were in advanced stages.

The severity of the bleeding as indicated by the blood count was evident in 22 patients in whom the hemoglobin on admittance to the hospital was below 10 grams and in 29 others between 10 and 12 grams; the remainder were above 12. The lowest recorded hemoglobin was 4.8 grams in a patient bleeding from a uterus slightly enlarged by multiple fibroids. In general transfusions of compatible citrated blood in amounts sufficient to raise the hemoglobin to at least 11 grams were given prior to operation.

The preoperative diagnoses (Table III) were confirmed at operation and by pathologic examination in 97 (72.4 per cent). No serious errors in diagnosis were made and no patient was operated upon unnecessarily because of an inaccurate diagnosis. Five patients were suspected of having corpus carcinoma as a cause for irregular and increasing bleeding but diagnostic dilatation and curettage and subsequent hysterectomy failed to confirm the presence of malignancy. Three of the 23 patients in whom the preoperative diagnosis was functional climacteric bleeding had adenomyosis and another a pedunculated submucous fibroid. In the remainder either those considered to have leiomyomas had adenomyosis, endometriosis or functional bleeding, or those suspected of having adenomyosis had fibroids. It is of interest that a total of 28 unsuspected pelvic lesions in addition to those diagnosed clinically were found at operation (Table IV).

TABLE III. BENIGN CLIMACTERIC BLEEDING. PREOPERATIVE DIAGNOSES

Leiomyomas	93
Functional bleeding	23
Endometriosis	12
Corpus carcinoma	5
Questionable	1

Since an important reason for the surgical treatment of bleeding at this age is that ovarian tissue may be conserved it is necessary to consider in more detail the 29 (22 per cent) in whom bilateral salpingo-oophorectomies were carried out at the time of hysterectomy. In 7 of the 29 a definite history of hot flushes was recorded on the chart and of the 6 women under the age of 45 who were castrated, bilateral pelvic inflammatory disease was found in one and extensive ovarian and pelvic endometriosis in two others. Twelve were over 50 years of age and the procedure apparently was done "prophylactically." In the rest the reason for removal of both ovaries is not clear. In 105 one or both ovaries were left in place at operation since there was no obvious reason for their removal.

TABLE IV. BENIGN CLIMACTERIC BLEEDING. UNSUSPECTED LESIONS FOUND

Adenomyosis	16
Endometriosis	6
Tuboovarian disease	4
Submucous fibroid	1
Radium ulceration	1

Total abdominal hysterectomy was performed in 121 (90.2 per cent), subtotal abdominal hysterectomy in 5 (3.6 per cent) and vaginal hysterectomy in 8 (6.2 per cent); an associated vaginal plastic procedure was done in 7 of those operated upon abdominally. Removal of the uterus was preceded by diagnostic dilatation and curettage in those patients in whom there had occurred

any intermenstrual bleeding or irregularity in spacing of the periods of flow. In some who had noted simply an increase in the amount of bleeding without alteration of the cycle or intermenstrual discharge this step was omitted; however, the uterus was opened and examined by the surgeon before the abdomen was closed. There were no deaths and the postoperative complications are enumerated in Table V. The complications were by and large less severe than in the other group, but this is not surprising because the lesions which indicated removal of the uterus were less serious and in many patients of shorter duration. The vaginal cuff and abdominal wound infections were mild and localized and responded promptly to evacuation. Wound bleeding was moderate in one patient in whom prophylactic administration of Dieumarol was begun the day of operation; the others were simply small hematomas. The potentially serious complications of wound dehiscence and pneumonia are much more disturbing but careful examination of the charts revealed no obvious reasons for their occurrence. The latter patient had been operated upon under spinal anesthesia and did not aspirate as far as can be determined. In each of those in whom the wounds separated the preoperative blood count had been adequate as was also the general health of the patient. Each abdominal incision had been closed with catgut in the peritoneum and interrupted steel wire in the fascia.

TABLE V. BENIGN CLIMACTERIC BLEEDING. POSTOPERATIVE COMPLICATIONS

Urinary tract infection	8
Vaginal cuff infection	3
Wound bleeding	3
Wound infection	2
Wound dehiscence	2
Pneumonitis	1

Comment

Although the need for control of abnormal climacteric bleeding occurs in about 14 per cent of women, it almost never is of such an urgent nature that careful and complete evaluation of the entire problem must be omitted. The two major considerations necessary for the formulation of a therapeutic program are to establish beyond question of doubt (1) that the bleeding is the result of a benign not a malignant lesion, and (2) that the quantity of blood lost has been or will be if it continues sufficient to interfere with the well-being of the patient. Thus the collection of specific information detailing the type and amount of bleeding, the duration of its deviation from normal, and its relationship to such external influences as trauma and medication constitutes the initial approach. A complete physical and pelvic examination supplemented by any laboratory studies which may be necessary to rule out or to evaluate systemic disease will aid both in determining the cause of the bleeding and in the plan for therapy. Complete blood studies will not only aid in confirming the history of blood loss but may in some instances indicate more profuse bleeding than is suggested by the patient's story. Evaluation of a patient whose periods increase in amount or duration of flow, in whom the interval between periods decreases, or who has intermenstrual bleeding or discharge is incomplete unless every effort is made to eliminate cancer by admittance to the hospital for careful examination and curettage under anesthesia and the investigation of any cervical lesion by biopsy.

While the cause for abnormal bleeding during this age period must be established in each instance, it does not necessarily hold true that every patient requires treatment, in fact those whose blood loss is of an amount demanding control are in the minority. During the period included in this study 328 additional women in the same age group were admitted to the Temple University Hospital for diagnostic dilatation and curettage and in most instances cervical biopsy, but in none was loss of blood thought to be sufficient to require more than accurate diagnosis. Those in whom the bleeding must be controlled are selected on the basis of a history of a definite increase as compared with their normal cycles proved either by direct observation or by a reduction in blood count and usually by the presence of pelvic pathologic changes although severe hemorrhage may occur with minimal palpable change. A slight to moderate increase in flow or alteration in regularity of the cycle is usually inconsequential and after malignancy has been eliminated any treatment except reassurance, general supportive therapy, and repeated examination is contraindicated. This holds true not only for the patient without gross pelvic abnormality but for those with fibroids smaller than a uterus at the twelfth week of pregnancy. Bleeding which initially is unimportant may gradually increase to an amount demanding control, hence these women must be examined at intervals no longer than 3 months until the bleeding has ceased completely. Each patient must be impressed with the fact that any increased bleeding or its recurrence after the menopause is to be reported at once and that follow-up examinations for the rest of her life are important.

After the need for therapy has been established, one must next consider methods by which blood loss can be controlled. For all practical purposes treatment with endocrine preparations is unwarranted because the bleeding, in the absence of pelvic disease, is an expression of early ovarian failure, the progression of which cannot at this time be prevented. Since the abnormality so frequently indicates irregularity in ovarian function and since gonadal rejuvenation is not possible, the bleeding must be stopped completely and permanently; hence effectiveness of therapy is a major consideration, but safety cannot be ignored, for treatment which controls the blood loss while subjecting the patient to a mortality rate far greater than that from the lesion cannot be considered.

Because of a high surgical mortality, the majority of such problems have in the past been managed by irradiation castration rather than by removing the uterus. Williams³ analysis of deaths following hysterectomy at the Philadelphia General Hospital between 1931 and 1941 is typical of the results of that period. In 1,870 such operations there were 52 deaths, a mortality rate of 2.77 per cent; 42 of these, however, should be preventable today since they were attributed to blood loss or infection, 9 others occurred in patients with cardiac lesions, and 1 was from the anesthetic. The current mortality for hysterectomy in general should be less than 0.5 per cent if advantage is taken of all the available refinements in preoperative preparation and postoperative care and if the patients are properly selected for the operative procedure (Campbell⁴ and Falk and Bunkin⁵ 0.2 per cent for vaginal hysterectomy, Danforth⁶ 0.4 per cent, and this study 0.13%). For climacteric bleeding the

death rate should be at its lowest, since operation can be reserved for those who are in good physical condition and who require little preoperative treatment other than replacement of blood, the time for operation may be selected since it rarely is an emergency, and because there almost always is comparatively minor organic pelvic disease.

Deaths from ovarian irradiation to control bleeding are rare if the patients are carefully selected for the procedure and if the treatment is properly administered and from this standpoint alone castration is superior to hysterectomy. The sudden precipitation of menopausal symptoms and the atrophic changes in the genital tract, both of which at times appear more severe than after the natural menopause, may be most undesirable for the physiologically young woman and since castration must be complete and permanent these side effects cannot be avoided. Substitution for the inactivated ovary is always less satisfactory than is the utilization of its normal secretion and not infrequently unless carefully managed is associated with reactivation of the endometrium and bleeding. Thus, for the patient in whom subjective symptoms of ovarian failure are not already present, castration may add a complication which to her is more serious than bleeding.

In addition to the solution of the immediate problem, a long-range view must be taken. Corseaden and Gusberg,⁷ in 1,100 patients irradiated for benign climacteric bleeding, noted that 15, or 3½ times the expected number, subsequently developed corpus carcinoma. Randall,⁸ in a similar study, also calculated the incidence of malignancy in his patients to be increased 3½ times. Speert and Peightal⁹ found that 21, or 9 per cent, of 270 patients with endometrial cancer had had previous irradiation for benign lesions; in 3 the malignancy was diagnosed less than 1½ years after therapy and may conceivably have been present but unsuspected. Randall also stated that in 35 per cent of his patients with corpus carcinoma menstruation had continued after the age of 50 years, whereas in 92 per cent of a group of postmenopausal women who had not developed such a lesion the periods had ceased before that age. Speert, on the other hand, is not impressed by the relationship between duration of menstrual life and development of cancer. While these figures cannot be utilized without reservation in making a choice between hysterectomy and irradiation for the control of bleeding, they suggest that retention of the uterus may not always be wise. The possibility that cancer *may* develop is never an indication for hysterectomy unless the amount of bleeding is sufficient to demand treatment or unless some other valid indication for surgery is present, therefore it is only to be considered as an alternative to irradiation castration and not as a necessity for every individual near the menopause in whom there is a slight increase in uterine bleeding.

While castration may be the preferable method for controlling bleeding in some patients there are others in whom it is hazardous and in these hysterectomy is to be preferred. Among the contraindications to irradiation are:

1. *Age:* There can be no arbitrary age limit after which ovarian function is no longer important, hence for each individual the primary consideration must be of physiological rather than chronological age. Certain women at 45 with subjective menopausal symptoms may be suitable for irradiation whereas in others physically much younger at 50 preservation of gonadal function may actually be more conservative. In general the patient with subjective symptoms of ovarian failure suffers little by castration but if she is free from these

symptoms removal of the uterus may be the preferable method for controlling the blood loss.

2. *Symptoms other than bleeding:* Small fibroid tumors which because of their size might not contraindicate irradiation for the control of bleeding can by virtue of their location or because of degeneration or infection produce symptoms unrelated to blood loss; such symptoms represent an indication for hysterectomy.

3. *Ovarian pathologic conditions:* The nature of ovarian neoplasms cannot be determined by the usual pelvic examination and since they are not destroyed by irradiation the presence of such growths is an indication for the surgical removal of the tumors and at the same time the uterus to control the bleeding. Nonneoplastic ovarian lesions make up 97 per cent of the enlargements under 5 cm. in diameter¹⁰ and thus a slight increase in size of the ovary does not in itself demand primary surgery, but certainly any tumor over 5 cm. in diameter is a definite contraindication to irradiation.

4. *Inflammatory lesions:* Old pelvic inflammatory disease, either gonorrhreal, postoperative, or postabortal, often is associated with the extensive formation of pelvic adhesions; adherent loops of bowel may be overirradiated and become necrotic. Infection in the cervix or the uterus may extend laterally and produce a pelvic cellulitis following pelvic irradiation by radium. Despite the fact that either of these complications is less likely to follow external irradiation than radium, such patients are better operated upon.

5. *The type of tumor and the size of the uterus:* The effectiveness of radium for controlling bleeding depends primarily upon its action upon the ovaries, hence if the uterine wall is so thickened that an insufficient dosage reaches the gonads, incomplete castration and continued irregular bleeding may result. Although this is not true of deep x-ray therapy the size of the uterus is of importance in selecting treatment, particularly if there are symptoms other than bleeding; some atrophy both of the uterus and fibroid tumors is expected after the menopause but the amount cannot be anticipated, hence relief from symptoms dependent upon reduction in uterine size is unreliable. Most uteri enlarged by tumors to a size greater than that of a 12 weeks' gestation should be removed rather than irradiated because tumor degeneration may follow the decreased blood supply thus making a later operative procedure necessary. Pedunculated tumors in general are better managed by surgical removal, the subserous ones because of the possibility of torsion and the submucous type because of potential infection, necrosis, and continued bleeding.

6. *Other surgical lesions:* A vaginal relaxation or prolapse requiring surgical correction is ordinarily an indication for hysterectomy if the bleeding is sufficient to require control since the uterus can be removed vaginally as part of the indicated operative procedure.

7. *Radiophobia:* In the minds of certain women irradiation and cancer are so firmly associated that it is impossible for them to believe that benign conditions can also be treated by this medium. If the patient cannot be convinced of the benignity of the lesion its removal may be preferable.

8. *Availability of irradiation:* The administration of radium and x-ray must be controlled by individuals experienced both in calculating their dosage and with their effects. Carelessness in irradiation can lead to untold damage which in the long run may endanger the patient more than primary hysterectomy. If an inexperienced individual must rely upon a commercial source to supply both radium and the directions for its use, this means of treatment is contraindicated.

If irradiation is contraindicated then in general hysterectomy is the method of choice for the control of bleeding. The reverse however is not necessarily

true, i.e., if irradiation can be administered removal of the uterus is not to be considered. The growing safety with which hysterectomy can be performed, the desirability of preserving ovarian function and the increased possibility that malignancy may develop in the uterus retained after abnormal climacteric bleeding have multiplied the number of these problems which are solved surgically. Despite the fact that the mortality following hysterectomy in the healthy woman with a small uterus and a clean pelvis is minimal, it cannot be recommended without careful consideration.

Among the contraindications to hysterectomy in patients in this age group are:

1. *The absence of a well-founded indication:* As emphasized previously, the fact that a slight increase or irregularity in menses occurs does not mean that treatment in any form is necessary. Prophylaxis against the future development of uterine cancer cannot be used alone in such patients as a reason for removing the uterus.

2. *The physical condition of the patient:* Although many medical conditions such as uncomplicated hypertension, diabetes, or mild cardiac lesions do not interfere with necessary surgery others may. For the patient with advanced cardiovascular renal disease, uncontrolled diabetes, or blood dyscrasias which may limit the life expectancy to a few years, hysterectomy is contraindicated. In fact, in such patients irradiation may be administered to control bleeding even though it ordinarily might be considered undesirable; for instance, x-ray might be chosen for an individual 40 years of age with severe chronic glomerulonephritis to control bleeding associated with a fibroid rising well above the pubis. The hazard of abdominal pelvic surgery in the presence of extreme obesity is definitely increased and in some instances dilatation and curettage and the insertion of radium into the uterus offer the lowest morbidity rate. Such abnormal thickness of the abdominal wall will, of course, contraindicate x-ray as well as surgery.

3. *The available facilities:* If hospital facilities do not permit safe surgery, removal of the uterus for benign bleeding is contraindicated. Necessary aids to the surgeon include a reliable laboratory, adequate surgical assistance, safe anesthesia, a dependable source of blood, and a staff sufficient to insure the best postoperative care for the patient.

4. *The surgeon:* As in the administration of x-ray and radium, hysterectomy by the inexperienced surgeon carries a potential mortality higher than that from bleeding. If the operation cannot be done safely and if there are no facilities for irradiation the patient should be sent elsewhere for the solution of the problem.

Although the contraindications are frequently more important than indications in determining both the need for and type of treatment, there must always be a reason for carrying out any procedure. The indications for surgery for the control of bleeding in women between the ages of 40 and 55 years are:

1. *Bleeding from a benign lesion in an amount sufficient to require its control.* As discussed above, the amount of bleeding must be evaluated not only by the history but by observation and preferably by the demonstration of a depressed blood count.

2. *Bleeding requiring control and associated with any lesion or condition contraindicating irradiation.*

3. *Bleeding which by reason of physician ability or physical facilities can be controlled more safely by surgery than by radiation.*

4. *Bleeding from a uterus which may be removed in conjunction with an indicated vaginal plastic procedure.*

Despite the fact that there may be a well-founded indication for hysterectomy and no definite contraindication, certain requirements must be fulfilled before one can feel justified in proceeding with the operative procedure. If the following requirements for hysterectomy cannot be met surgery is hazardous:

1. *Careful preoperative evaluation* to substantiate the need for surgery and to determine whether or not such a procedure is safe.
2. *Replacement of blood* before the operation to a level of at least 11 grams of hemoglobin.
3. *Careful study to rule out cancer* as the cause for bleeding by dilatation and curettage and frequently cervical biopsy, and, of utmost importance, by microscopic evaluation of the tissue by a competent pathologist.
4. *Selection and administration of the anesthetic* most suitable for both the operative procedure and the patient.
5. *An adequate operation.* In most instances total hysterectomy is to be preferred to the subtotal procedure because of the annoying benign and the potentially lethal malignant lesions which may develop in the retained cervix. There is no question but that the total operation may be associated with an increase in both morbidity and mortality particularly when done by the inexperienced surgeon, but if the utmost benefit is to be derived from removal of the uterus the cervix cannot be left unless its extirpation adds materially to the risk. Since one of the major reasons for hysterectomy as contrasted to irradiation is the preservation of ovarian function, one or both ovaries should be left if there have been no subjective menopausal symptoms. "Prophylactic" removal of normal functional ovaries in the physiologically young woman is unwarranted since true ovarian neoplasms developing in normal ovaries left at the time of hysterectomy are rare.¹¹ On the other hand in postmenopausal women or those with symptoms of ovarian failure in whom hysterectomy is indicated there appears to be no reason for the conservation of ovarian tissue.
6. *A competent surgeon* who is capable of evaluating the patient and carrying out the required operative procedure safely and who is prepared to proceed with any type of abdominal or vaginal hysterectomy which is indicated rather than to subject all patients to the one operation he has learned to do. It has been said that the "occasional operator" should confine his pelvic ventures to subtotal rather than to total hysterectomy. It is our opinion that one so unfamiliar with pelvic surgery that the only operation at his disposal is the removal of the top of the uterus by the same token may not have sufficient judgment to determine whether there is a logical indication for hysterectomy and should refer his patients to someone more experienced in the evaluation and treatment of pelvic disease.
7. *Careful postoperative care* including thorough investigation of temperature elevations or unusual symptoms with prescription of antibiotic and chemotherapeutic agents only as indicated after such investigation, the replacement of blood when necessary, and supervised exercise and ambulation will prevent most postoperative complications both major and minor and will reduce both surgical mortality and morbidity.

Despite all the factors which make the end result from removal of the uterus more desirable than the destruction of the function of the ovaries the risk from hysterectomy is unquestionably greater than that from irradiation and cannot be disregarded. No matter how uncomplicated the procedure and how skillful the surgeon the potentially lethal complications from abdominal surgery are always present, hence the decision to remove the uterus cannot be made without just reason. Our aim for the solution of this and every other gynecological

condition which today is so crudely managed either by destroying or removing the malfunctioning organ or (as in this instance) its target tissue must be to attack the cause. While prevention or physiological correction is unquestionably the ultimate goal we must at this point solve each problem as adequately as we are able and for bleeding near the menopausal period the choice lies between castration and hysterectomy. When such bleeding is sufficient to demand control the authors prefer to perform total hysterectomy either abdominally or vaginally if the risk from such an operative procedure is minimal and in a physiologically young woman because (1) bleeding can be controlled permanently without suddenly precipitating the menopause, (2) any symptoms associated with subsequent cessation of ovarian function may be treated without fear of producing reactivation of the endometrium with bleeding, and (3) the development of uterine cancer which may be increased in these patients is prevented. We do not intend this to be a recommendation to extend the indications for treatment in women of this age group but rather to alter the therapy in some of those who in the past might have been castrated. If sufficient effort is directed toward careful evaluation of each individual patient before treatment is instituted the total number either irradiated or operated upon can be reduced. There is no evidence to support the thought that the wholesale "prophylactic" removal of the uterus in every patient who develops a slight increase in bleeding at the climacteric period will improve the over-all mortality rate. The surgical deaths would of necessity increase and might well outweigh the loss of life due to the later development of cancer. More thorough appreciation by women and their physicians of the value of diagnosis and prompt treatment of uterine cancer in its earliest form is, until prevention becomes possible, a safer and more logical approach to the problem.

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Discussion

DR. CARL P. HUBER, Indianapolis, Ind.—In the present presentation it is suggested that total hysterectomy with preservation of the ovaries and their function is a more conservative treatment of benign uterine bleeding in the woman between 40 and 55 years of age than irradiation. Support for this thesis is derived from a commendably negligible mortality associated with present-day total hysterectomy. The fact that an operative procedure is safe is insufficient reason for recommending it. Cesarean section is also performed with an extremely low mortality rate but is not recommended as the solution to all obstetric problems. Actually, both the cesarean section rate and that of hysterectomy are subjected to greater criticism than is directed toward other obstetric and gynecologic procedures. Definite indications should be established for each.

Removal of the normal uterus in order to prevent the development of carcinoma of the cervix or endometrium is an unsound argument. The patient whose ovaries are present requires careful periodic examinations as does the postmenopausal patient who has a normal uterus. In neither group is the frequency of carcinoma great but it is equally unpredictable.

The preservation of ovarian function in a physiologically young woman is a sound argument in favor of hysterectomy in this group of patients. The majority of such patients will be nearer the age of 40 than 55 years. The deliberate destruction of ovarian function in such individuals is psychologically dangerous. One should not ignore the psychological damage which may be associated with hysterectomy even with ovarian conservation.

In many instances, in the age group under consideration, thorough curettage with careful microscopic examination of the endometrium is sufficient to eliminate the presence of malignancy and subsequent bleeding is insufficient to warrant additional therapy. Endocrine therapy while incapable of producing normal ovarian function in this age group may be effective in controlling sporadic episodes of abnormal bleeding and should not be entirely ignored.

DR. HERBERT SCHMITZ, Chicago, Ill.—I would like to agree with Dr. Huber and to re-emphasize the statement that he made relative to the necessity of a careful follow-up of patients despite the fact that the uterus has been removed. Such a patient not only has ovaries remaining which may subsequently undergo degeneration and malignant change, but she has breasts which are frequently the site of serious difficulties and should be periodically examined along with the remaining ovaries. I would prefer that the uterus, if normal, be retained by the patient, because then she would not be laboring under a false impression that she is free of possible difficulty, and, therefore, not return for follow-up examinations and thus deprive herself of the advantages of periodic examinations of her pelvic organs and breasts.

I would like to question the advisability of performing a diagnostic curettage when immediate total abdominal hysterectomy is to be performed. I do not believe that the information obtained by this method and frozen section is of any value if the uterus is to be removed, regardless of the findings. It would be much more satisfactory to open the uterus immediately after its removal without having previously disturbed the uterine cavity. Then, if examination reveals carcinoma, removal of the tubes and ovaries and other structures indicated by the findings can be carried out.

If one adopts the method of treating endometrial carcinoma with preoperative irradiation, then curettage followed by immediate radium sterilization of the tumor is an accepted procedure. If the subsequent tissue examination shows that there is no malignant change in the tissue removed, then the irradiation has been adequate to cause permanent cessation of the menstruation. The effect of irradiating the uterus is no more disturbing to the patient than the removal of the uterus. There is the same psychological disturbance in either instance. Menopausal symptoms are not severe following irradiation with radium in the uterine cavity, because all ovarian function is not destroyed. In our last report of some 500 cases treated with irradiation for benign bleeding, only 5 per cent of the patients required any subsequent treatment for the menopausal symptoms. All of our patients, however, are prepared psychologically for what is going to take place, and that is just as necessary if hysterectomy is to be performed.

DR. HANS KOTTMEIER, Stockholm, Sweden.—To Dr. Willson's interesting paper I would like to add some points of view based on our experience at the Radiumhemmet. I agree with Dr. Willson that patients in the preclimacteric age who have received roentgen sterilization treatment because of recurrent functional bleeding often have severe menopausal symptoms. This is particularly common in nervous patients. Roentgen sterilization is, therefore, only carried on in selected cases at the Radiumhemmet. However, menopausal symptoms sometimes also can appear after hysterectomy, as mentioned by American clinicians in particular. It is not always reasonable to perform either hysterectomy or

roentgen sterilization in a patient suffering from recurrent preclimacteric bleeding. We have treated more than 400 cases of this type with intracavitary radium. The indications for this treatment must be strict. Only patients in the preclimacteric age suffering from recurrent bleeding should be treated. A malignant tumor must be excluded as far as possible. We have tried to give the smallest dose which would give a favorable result, according to our experience. The dose we give is much less than that usually recommended in the American literature—40 mg. of radium element screened by 0.5 mm. of platinum. This is introduced into the uterine cavity from the fundus to the internal os for 16 hours. It is important to introduce the radium in direct connection with a curettage, carefully carried out.

The results of this type of treatment have been very satisfactory. If the result has not been what we expected, the indication for the treatment has been wrong. A submucous fibroid or an ovarian tumor—a granulosa tumor in particular—has been present in those few cases in which the radium treatment has not given satisfactory results.

Menopausal symptoms after this intracavitary radium treatment are slight and often do not appear for months or even years after uterine bleeding has stopped. Investigations as to the excretion of estrogenic and follicle-stimulating gonadotrophic hormone in the urine, as well as pathoanatomical studies on some ovaries removed by laparotomy six months to one year after the radium treatment, have proved that the endocrine-ovarian function is not much influenced by the radium treatment. The dose measured on the ovaries varies in different points between 250 and 100 r. According to my experience I would like to recommend this treatment in patients in the preclimacteric age suffering from recurrent functional bleeding.

DR. EMIL NOVAK, Baltimore, Md.—There are always a number of therapeutic problems in gynecology which are in a more or less fluid state and concerning which no one can assume a very oracular role. The most important one is of course that of the treatment of carcinoma. The question of the treatment of benign bleeding in women at or near the menopause appears also to have become more than formerly fluid. Until very recent years most of us were more inclined to irradiation once the diagnosis has been made by diagnostic curettage, and that is still my practice, although hysterectomy must be the sensible choice in certain cases, as where there exists some other valid indication for laparotomy. Curettage itself, for that matter, when done for diagnostic purposes, is not infrequently curative as well, many women going on quite normally, without further treatment. On the other hand, there are frequent recurrences.

Within recent years a good many gynecologists have become much more radical, many having in mind the possible development of adenocarcinoma in later life. This apprehension is based on a number of reports, chiefly those of Corseaden and Randall, but I believe these need confirmation, and they do not conform to my own experience or to that of some others with whom I have discussed the subject. A recent article by Foulkes in the *Journal of Obstetrics and Gynaecology of the British Empire*, reporting on the study of a good many cases, gave results not in conformity with those I have mentioned in this country. Most of us feel that hysterectomy is already a widely abused operation, and I do not believe we would wish to encourage this abuse. In this field there is still ample opportunity for individualization of treatment. If a climacteric woman has functional bleeding but absolutely no structural abnormalities, I would not subject her to even the slight hazard of hysterectomy if I could cure her with irradiation. But if she has a recurrent appendicitis or a ventral hernia, or some other condition also, I would include hysterectomy in the operative procedure. The indication for hysterectomy is clearer in the woman below the age of 40 who has intractable bleeding, for a patient at that age can spare her uterus much better than her ovaries.

Whether adenocarcinoma is actually more frequent after irradiation for menopausal functional bleeding I do not know, although this has not been my own experience, and I do not see why it should be so. It would seem wise to go slow in advocating hysterectomy as the best routine plan in the management of this disorder. Such a recommendation would save

the conscience and simplify the problem of the general surgeons who do such a large proportion of the hysterectomies in this country. At any rate, while there may be some justification for this surgical resurgence taking place in this field, I do not think we should be too quick to advise surgical treatment for benign menopausal bleeding.

PROF. JAMES YOUNG, London, England.—Dr. Novak has referred to the work done by Foulkes in my department and I thought I might be justified in occupying your attention for only a few minutes to amplify the statement which he made. As the result of an investigation carried over a considerable number of cases, Dr. Foulkes tried to assess the influence of curettage in regard to the control of dysfunctional bleeding. We selected only those cases in which gross abnormality was not present and we satisfied ourselves that we had statistical evidence to prove the following points:

1. In the younger women the results of curettage were relatively unsatisfactory. In only a relatively small portion—30 per cent—was the follow-up found to demonstrate there had been adequate relief.

2. In the older women, on the other hand, the result of curettage was in a very high proportion of the cases successful. We were able to satisfy ourselves that in at least 60 per cent of women nearing the menopause curettage was associated with relief which could be described as clinically adequate.

DR. WILLSON (Closing).—I do not consider hysterectomy to be the only method for treating these patients. I still would reserve radiation for a selected group of patients in whom it is safer or in whom hysterectomy is contraindicated. During the three-year period of this study, as is noted in the body of the paper, there were 328 other women of the same age admitted because of irregular bleeding but in whom only dilatation and curettage were done. In these the bleeding was insufficient to require anything other than accurate diagnosis. We do not operate on every patient who has a little irregularity near the menopause but we do insist that each patient who has a menstrual irregularity have malignancy eliminated as completely as possible. If we suspect corpus carcinoma at the time of dilatation and curettage, we await the microscopic report which is available within twenty-four hours, and hysterectomy is usually then done. There is no prolonged period of waiting and we are aware of no trouble as a result of that practice. All the uteri are opened at the time of operation and, if there is any suggestion of corpus carcinoma that might have been missed by curettage, the adnexa are removed.

We are not disturbed about the development of ovarian carcinoma in retained ovaries because in our experience the growth of a true ovarian neoplasm in an ovary after hysterectomy is not a very serious problem. It occurs rather uncommonly.

The breasts are another matter. They should be examined at regular intervals in every woman as well as after either hysterectomy or castration.

TUBAL STERILIZATION*

FREDERICK C. IRVING, M.D., BROOKLINE, MASS.

(From the Department of Obstetrics, Harvard Medical School and Boston Lying-in Hospital)

MANY failures of tubal sterilization have been reported in recent years, most of them following the procedure described by Madlener¹ in 1919. In his original operation a knuckle of the Fallopian tube is crushed by a heavy clamp, the clamp removed, and a silk ligature applied to the crushed area. Walthardt² modified this technique by crushing and ligating both arms of a longer loop, but in neither instance was the knuckle or loop excised. At first the original operation and its modification appeared to be effective, for in 1932 Madlener³ reported 166 cases operated on in 22 years without a known failure; and the next year Gianella,⁴ who introduced a further change by suturing the crushed portion of the tube beneath the round ligament, was able to collect 604 cases with only one subsequent pregnancy. More recently, however, numerous unsuccessful cases have appeared in the literature. Rubovitz and Kobak⁵ reported subsequent pregnancies in 5.3 per cent, Dippel⁶ in 4.9 per cent, Pfeutze⁷ in 1.8 per cent, Dieckmann and Hauser⁸ in 3.6 per cent, and Darner⁹ in 8.2 per cent, while Schultze¹⁰ collected 32 instances of failure and added 2 of his own in an unrecorded number of operations. In view of these unsatisfactory results, it appears that the Madlener operation or any modification of it does not provide enough insurance against future pregnancy to justify its performance. In fact, until the Pomeroy operation came into use all operations upon the tubes to produce sterility were notoriously ineffective. As long ago as 1921 Flatau,¹¹ who viewed the situation with extreme pessimism, maintained that up to that time 42 different techniques had been devised and that all had failed. In a paroxysm of frustration he freed the tubes from their attachments and tied knots in them. He performed this bizarre operation on 6 patients but did not report the outcome, nor does anyone else appear to have resorted to this curious device.

The method of Pomeroy as described by Bishop and Nelms¹² is as simple as the Madlener operation, if that is all one desires, and much more effective. The loop of tube is not crushed but its arms are tied together with an absorbable suture and the portion of the loop beyond the ligated area is excised. The authors reported 60 cases without failure. Lull¹³ reported 589 successful cases treated in the same way, Knight¹⁴ 175 cases with one failure, and Darner⁹ 141 cases with no failures. In 1947 Nelms and Doyle¹⁵ recorded 404 cases with only one unsuccessful result, but that was a ruptured extrauterine pregnancy. Another ectopic gestation following a Pomeroy sterilization was reported by Lutz.¹⁶ Nelms and Doyle stated that one of their patients had intestinal ob-

*Read before the Seventy-Third Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. V., May 11 to 13, 1950.

struction and another a secondary hemorrhage from slipping of the ligature. It seems, therefore, that while the Pomeroy method is a vast improvement upon that of Madlener, it by no means gives absolute security against another pregnancy nor is it always free from serious complications.

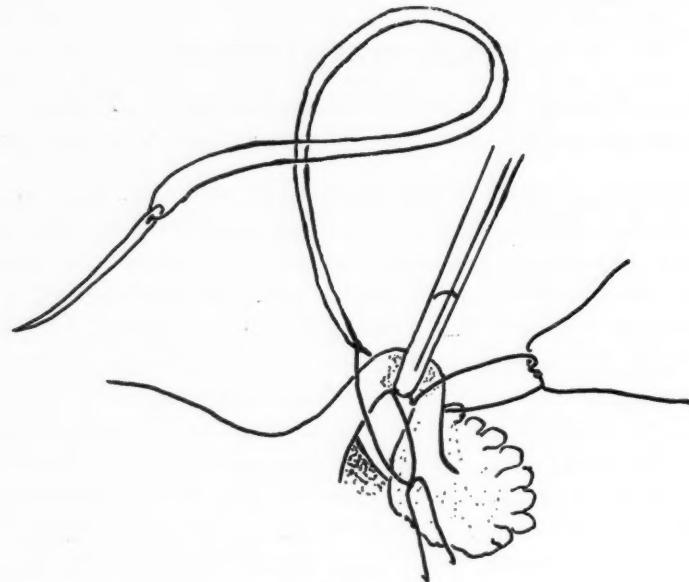


Fig. 1.

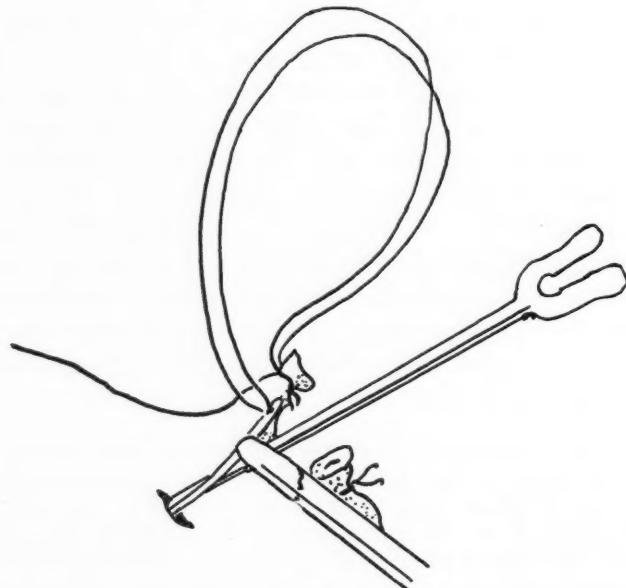


Fig. 2.

The cause of failure in both the Madlener and Pomeroy methods is of course the possible formation of a false ostium in the proximal portion of the ligated tube. To prevent this accident the writer¹⁷ devised the operation, first published in 1924, which is performed as follows: One and one-half inches

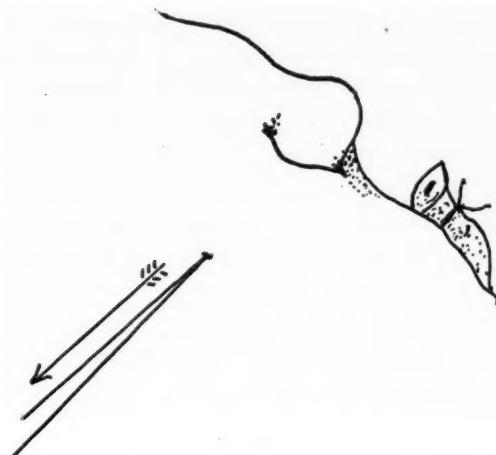


Fig. 3.

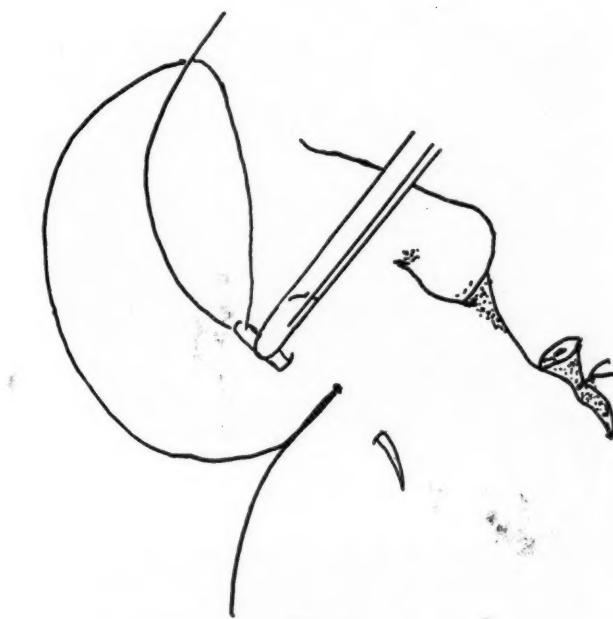


Fig. 4.

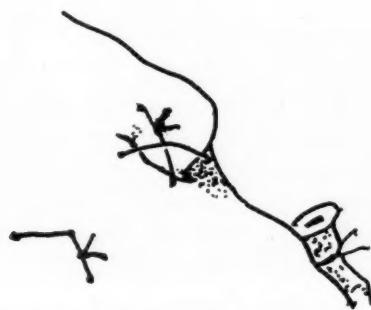


Fig. 5.

from its cornual insertion, the tube is elevated in the bite of a clamp. The mesosalpinx beneath this point is pierced by a hemostat in a bloodless area. The distal portion of the tube is ligated with No. 1 chromic catgut. Proximal to this a double suture ligature of the same material, mounted on a half-curved, round-pointed needle and knotted about three inches from its ends, is tied about the tube which is divided between the two ligatures (Fig. 1). A stab wound is made in the myometrium at the proximal end of the tube. A sharp-pointed hemostat is plunged into the uterine wall through this stab wound as far as its lock and its tips spread, thus making a pit. A grooved director is inserted in this pit as far as it will go and the half-curved needle on a needle holder is passed along the director to the extreme depth of the pit and is brought out on the surface of the uterus (Fig. 2). The director is removed.

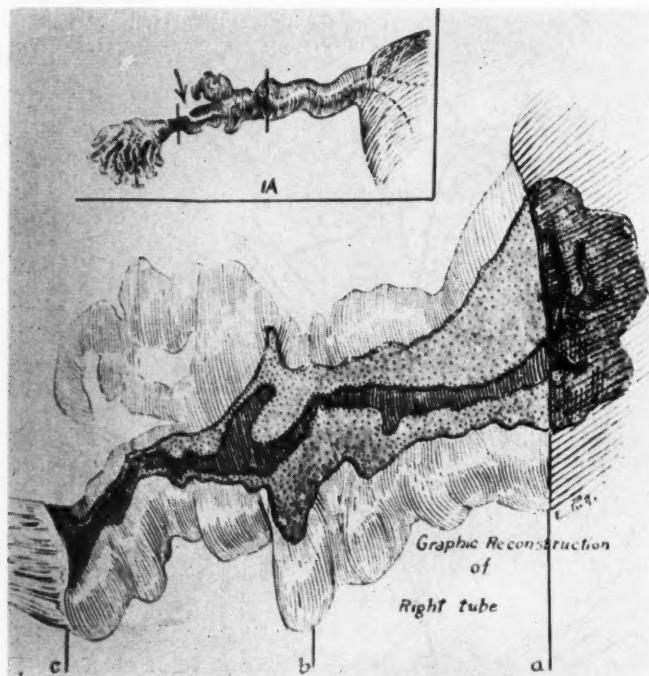


Fig. 6.—Graphic reconstruction of a portion of the right Fallopian tube from a case of failure of Pomeroy sterilization showing the connection by sinus formation between its lumen and the peritoneal cavity. The insert 1A shows the part selected for microscopic study. (Fox, F. H.: Surg., Gynec. & Obst. 71: 462, 1940. Reprinted by permission.)

Traction on the suture ligature causes the tube to enter the pit for approximately three-quarters of an inch (Fig. 3). One strand of the double suture ligature is cut, a cross-stitch is made in the superficial portion of the uterine wall, and the free ends are tied, thus anchoring the tube deeply in the myometrium (Fig. 4). The small wound at the point of entrance of the tube is closed with a figure-of-eight suture of chromic catgut, thus completing the operation (Fig. 5). The distal portion of the divided tube is not treated in any way; it is not necessary to bury its cut end in the broad ligament.

While this operation requires for its performance a few more minutes than does that of Pomeroy, it can be completed rapidly enough, and we be-

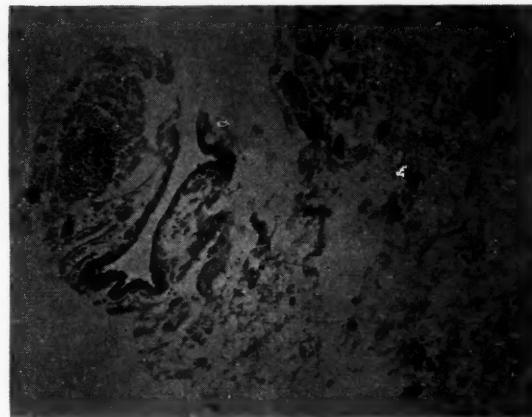


Fig. 7.—Photomicrograph of cross section taken at point *c* in Fig. 6 shows lumen opening into the peritoneal cavity. (Fox, F. H.: *Surg., Gynec. & Obst.* 71: 463, 1940. (Reprinted by permission.)

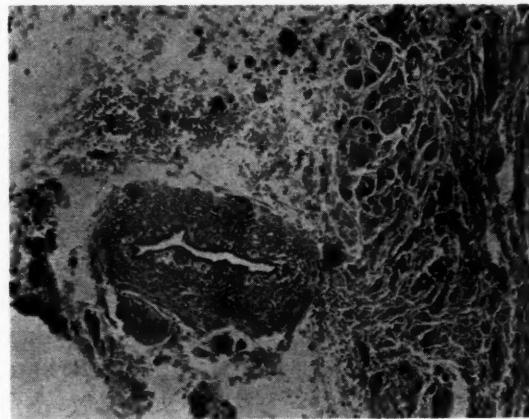


Fig. 8.—Photomicrograph of cross section taken at point *b* in Fig. 6. (Fox, F. H.: *Surg., Gynec. & Obst.* 71: 463, 1940. Reprinted by permission.)



Fig. 9.—Photomicrograph of cross section taken at point *a* in Fig. 6. (Fox, F. H.: *Surg., Gynec. & Obst.* 71: 463, 1940. Reprinted by permission.)

lieve that the patient's interests are better served by security than by haste. Since no vessels are divided, the bleeding is minimal. From Jan. 1, 1916, to Jan. 1, 1949, 814 patients have been sterilized by this method on the public wards of the Boston Lying-in Hospital by members of the visiting, resident, and house staffs and no failures have been reported. Moreover, there have been no subsequent extrauterine pregnancies, nor has it been necessary to reopen the abdomen because of postoperative accidents.

TABLE I. INDICATIONS

Previous cesarean sections	324	29.3 per cent
Rheumatic heart disease	270	24.4 per cent
Hypertension	102	9.2 per cent
Diseases contraindicating future pregnancies	84	
Relaxed pelvic floor	67	
Chronic nephritis	63	
Pulmonary tuberculosis	50	
Excessive multiparity	28	
Deformities or diseases of the bones	27	
Deformities or diseases of the pelvic soft tissues	25	
Mental deficiency	24	
Abnormalities of pregnancy or labor	18	
Rh-negative mother	17	
Congenital heart disease	7	
Total	1,106	

In 1940, Fox¹⁸ in our clinic reported 645 operations for sterilization of various kinds from 1916 to 1937. One of the purposes of the present paper is to add 461 similar cases which were operated on from 1937 to 1949 and thus cover the entire period of 33 years. The total number of operations for sterilization of all types is therefore 1,106. During this time there were 65,335 deliveries on the public ward service; the rate of sterilization was 1.7 per cent. In Table I are shown the reasons for sterilization. It will be noted that previous cesarean sections and rheumatic heart disease were the chief indications. It is our custom to offer a patient sterilization at the time of her third cesarean section but the point is not pressed.

TABLE II. TYPES OF STERILIZATION OPERATIONS

Bilateral Irving	814	75.5 per cent
Bilateral Pomeroy	118	10.7 per cent
Unilateral Irving combined with other methods	12	
Unilateral Pomeroy combined with other methods	3	
Hysterectomy	93	
Wedge-shaped excision	50	
Oophorectomy	6	
Salpingectomy	5	
Ligation of tubes	3	
Defunctionation of uterus	2	
Total	1,106	

Table II shows the methods used in these 1,106 cases to effect sterilization. Three-fourths of them, or 814, were sterilized by the writer's method. Two patients operated on by the Pomeroy technique subsequently became pregnant. Since there were 118 Pomeroy operations, our rate of failure with this technique was 1.7 per cent. One of these patients, a woman with rheumatic heart disease, had been delivered by cesarean section accompanied by a

Pomeroy sterilization. The following year she returned 4 months pregnant. An abdominal therapeutic abortion, a resection of the right tube well into the uterine cornu and an excision of the proximal portion of the left tube were performed. A graphic reconstruction of the right tube and microscopic studies of it were made by Fox, and I am indebted to her for the figures which follow. A false ostium was found at the point of ligation with a free opening between the peritoneal cavity and the proximal portion of the tube (Fig. 6). Microscopic cross sections of the tube at the points marked in the reconstruction are shown. Fig. 7 demonstrates the open sinus; Fig. 8 and Fig. 9 reveal a normal tube.

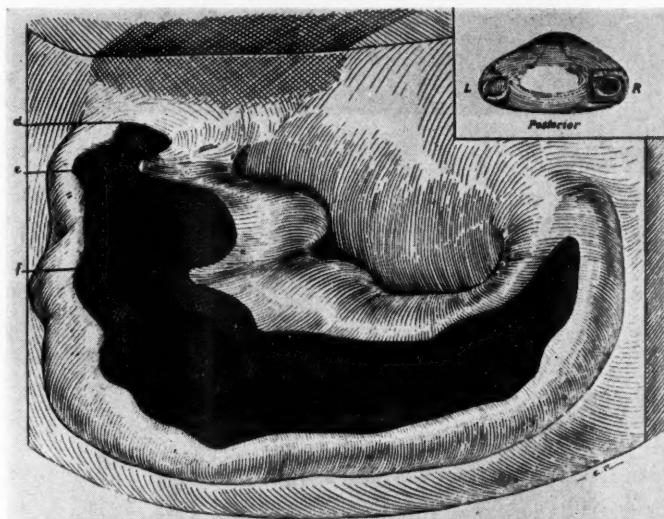


Fig. 10.—Graphic reconstruction of right cornu of uterus from a case of Irving sterilization, the anterior surface of the uterus lying to the right. The cross-hatched area at the upper left represents scar tissue in the uterine wall on the cut surface of the block of tissue at the point where the tube is buried in the uterine wall. Insert shows the position of the reconstructed block in relation to the uterus. (Fox, F. H.: Surg., Gynec. & Obst. 71: 466, 1940. Reprinted by permission.)

In the second failure, the patient was operated on by the Pomeroy method because of three previous cesarean sections. The next year she entered the hospital 8 weeks pregnant and a hysterectomy was performed.

Fox also made a graphic reconstruction of the right tube of a patient operated on by the writer's method in 1928. Eight years later a supracervical hysterectomy was performed because of fibroid tumors. Fig. 10 shows both tubes safely buried in the uterine wall. Fig. 11 demonstrates that the cut end of the tube is occluded by scar tissue in the myometrium. Fig. 12 and Fig. 13 show the normal histology of the rest of the proximal portion.

Data from the last 461 cases were obtained to indicate when the operations for sterilization were performed. Two hundred thirty-nine, or 51.8 per cent, accompanied cesarean section, 101, or 21.9 per cent, accompanied abdominal therapeutic abortion, 88, or 19.2 per cent, accompanied gynecological operations, 29, or 6.3 per cent, were post partum, and 4, or 0.8 per cent, where independent of operation or delivery.

For those curious about such matters it is significant to note that in the entire series of 1,106 patients, 677, or 61.2 per cent, were of the Roman Catholic faith, 318, or 28.8 per cent, were Protestants, 93, or 8.4 per cent, were Jewish, 17, or 1.5 per cent, were Greek Orthodox, and one woman had no religious belief at all.



Fig. 11.—Photomicrograph of cross section of the Fallopian tube taken at point *d* in Fig. 10.
(Fox, F. H.: Surg., Gynec. & Obst. 71: 466, 1940. Reprinted by permission.)



Fig. 12.—Photomicrograph of cross section of the Fallopian tube taken at point *e* in Fig. 10.
(Fox, F. H.: Surg., Gynec. & Obst. 71: 466, 1940. Reprinted by permission.)

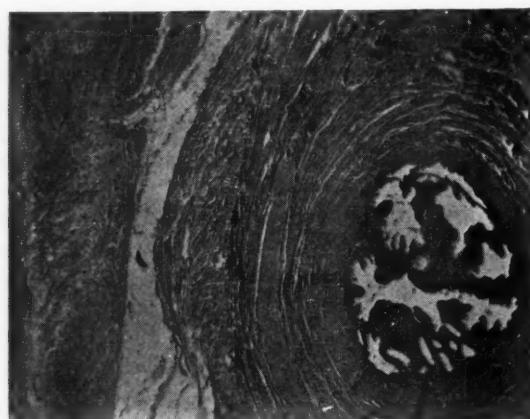


Fig. 13.—Photomicrograph of cross section of the Fallopian tube taken at point *f* in Fig. 10.
(Fox, F. H.: Surg., Gynec. & Obst. 71: 467, 1940. Reprinted by permission.)

Summary

1. The Madlener and Pomeroy methods of tubal sterilization are discussed.
2. All operations for sterilization on the public wards of the Boston Lying-in Hospital from 1916 to 1949 are recorded.
3. Two failures with the Pomeroy method are considered.
4. The writer's method of tubal sterilization is described and 814 cases operated on by this technique without a known failure are reported.

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1180 BEACON STREET

Discussion

DR. FRANCIS BAYARD CARTER, Durham, N. C.—Dr. Irving gives an impressive series of sterilization operations done on 1,106 women. Eight hundred fourteen patients were sterilized by the author's operation with no known failures.

He also reviews the literature concerning failures in tubal sterilization operations done with the technique of Madlener and with modifications of that technique. He states that, until the Pomeroy operation came into use, all operations upon the tubes to produce sterility were notoriously ineffective. The Pomeroy operation, however, fails to give absolute security against pregnancy and is not devoid of complications. In a series of 118 patients in his clinic, the percentage failure of the Pomeroy operation was 1.7 per cent.

His indications for sterilization were: repeat cesarean 29.3 per cent; rheumatic heart disease 24.4 per cent; hypertension 9.2 per cent. We were impressed by the figure of 270 patients with rheumatic heart disease. I would like Dr. Irving to give his present attitude to rheumatic heart disease in its various manifestations.

We were also impressed to note that 93 women had hysterectomies performed. In our own clinic, most of the patients who have true indications for sterilization are patients who have had many pregnancies. We like, whenever possible, to do vaginal rather than abdominal operations. We prefer in the age group of 35 years or above to do vaginal hysterectomy, with adequate anterior and posterior repair, if these be indicated, rather than submit these patients to abdominal operations. We also prefer to do any tubal sterilization operations by the vaginal approach whenever possible. The patients who have had sterilization either by the abdominal or vaginal operations with the uterus left in situ often develop subsequent minor and major pathologic conditions in the uterus. I would like to ask Dr. Irving if he has any statistics on complications following his operation or on the development in these patients of subsequent minor or major pathologic lesions in those uterus left in situ.

I would congratulate Dr. Irving on the fact that in 814 patients upon whom his operation was done there were no subsequent pregnancies.

DR. EDWARD L. KING, New Orleans, La.—We have had similar results with the use of the Madlener technique. We do sterilization operations at the Charity Hospital in cases of chronic hypertension, which is very common in the Negro race there, and we have noted failures. The residents have preferred the Madlener operation because it is quicker, but these figures make me stop and think. Just before I left New Orleans we saw a patient who was sterilized one year or so ago for chronic hypertension. She came in now in very serious condition, about six months pregnant, and developed a cerebral hemorrhage which would have been avoided if she had been sterilized properly.

I use the Irving technique quite frequently. I found that sometimes I had troublesome hemorrhage, but I may have gone too close to the tube and not far enough toward the body of the uterus. We have liked the Cooke technique very much in which the tube is buried in the upper surface of the round ligament. I have had one failure from that operation and Cooke thought I did not give enough slack.

We have also used hysterectomy in some of these cases but that is a more formidable procedure.

I would like to ask Dr. Irving about oozing at the time of sterilization with cesarean section. We do not find it so marked in postpartum sterilization as with cesarean section. We have also found that if we use a No. 000 atraumatic needle we have better luck.

PROF. TASSILO ANTOINE, Vienna, Austria.—At our clinic we use the Madlener method and we are satisfied with it. I have no figures to give you but I know we have over 200 cases with no failure. One of the advantages is that it is an absolutely bloodless operation, and we always do it by the vaginal route. We do this operation either alone or combined with interruption of pregnancy.

I would like to ask Dr. Irving if he does his operation per vaginam sometimes.

DR. C. FREDERIC FLUHMAN, San Francisco, Calif.—Since 1942 one of my colleagues at Stanford Hospital, Dr. Harold M. Lyons, has been interested in developing a new and simple method of sterilization. In his own words, "It was decided that thermal desiccation would produce death of all tissue to which it was applied. The point of application was to be at the available point of maximum narrowing. Palpation of the 'tubes' and close visual inspection plus the reviewing of microscopic cross sections makes it obvious that mass ligation or mass treatment of the tissues referred to and pictured as the Fallopian tubes is unnecessary. The majority of the substance removed at the time of tubal resections is composed of blood vessels, lymphatics, and packing tissue. The Fallopian tube itself is a firm cordlike structure of 1 to 2 mm. in diameter. The mobility of this cord between the leaves of the broad ligaments is alarming and probably the cause of many reported failures in the Madlener and Pomeroy procedures. The true functional cord is of approximate size, mobility and consistency of the vas deferens in the male. No physician would consider a vasectomy without isolating the vas from the surrounding blood vessels, lymphatics and packing tissue."

"In our method of sterilization the tube is isolated in its proximal portion by palpation, then three curved clamps without teeth are placed across the cord at intervals of 0.5 cm. The instruments are touched serially with the electro cautery and the tissue cauterized until complete tissue death is insured. This usually takes about three seconds to each instrument. The clamps are then removed with care to prevent tearing of the desiccated tissue. The average time taken to complete the procedure is about 75 seconds per side."

So far it has been employed in only 29 cases but there have been no failures. It was done in two patients after failure of a Madlener and a Pomeroy operation, respectively. Dr. Lyons hopes this procedure might be done with a culdoscope.

DR. IRVING (Closing).—Now that the discussion is over I am relieved because I had suspected that someone might turn up with a case in which this operation was done and the patient later became pregnant. Since that is not the case I am breathing more easily.

In regard to Dr. Carter's point: He noticed a large incidence of heart disease in our series and he wanted to know if we were still sterilizing as many patients with rheumatic heart disease. The answer is no. You must remember that this series goes back to 1916 which was before we had established the Cardiac Clinic at the Boston Lying-in Hospital. Since that time the number of patients sterilized for heart disease is few but in each instance the condition was serious. However, there is this to be said: We do have a great deal of rheumatic heart disease in the New England states, and we have a very active Cardiac Clinic. Naturally we would expect to have more cases of rheumatic heart disease than any part of the country where the climate is more benign.

As for hysterectomy, in the last part of the series none of the patients was sterilized by hysterectomy. That operation was done as far back as 1916 and usually because the patient had a fibroid tumor.

As for combining sterilization with plastic operations, this was done quite frequently, but, on the other hand, our clinic is chiefly an obstetric clinic and all the women operated upon were in the childbearing age; they came in for obstetric reasons and not for gynecologic reasons. Almost all of the gynecologic patients were old cases in which we had attempted to improve our lack of skillful handiwork in the past.

Dr. King is to be congratulated on his good results with the Madlener operation. I think they are better results than are being obtained elsewhere in this country. He seemed worried about oozing and so did Dr. Antoine who spoke of the Madlener technique being "bloodless." So it is, but the operation I advocate can be made bloodless if one avoids the blood vessels. That might be said of a number of operations. The tube with its attached mesosalpinx is brought into the wound; it is not divided and there is no opportunity for bleeding.

THE USE OF RADIOACTIVE COBALT IN THE TREATMENT OF CARCINOMA OF THE CERVIX*†

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THE applications of the radioactive isotopes for therapy in gynecologic malignancies have not been extensively discussed to date. Myers, working in our institution, first proposed radioactive cobalt as a therapeutic weapon¹ and delineated its properties and characteristics,² and the authors have previously outlined the radiologic considerations in therapy with Co-60.³ The present paper is concerned with the use of this particular isotope as an agent in the treatment of carcinoma of the cervix, considered primarily from the point of view of the clinician. Such a presentation must quite obviously be in the nature of a progress report, and many questions in connection with this work are as yet unanswered.

The application of any particular radioactive substance to the therapy of malignancies in the human being is inevitably affected primarily by the radiologic properties of the material involved. The properties of Co-60 which have influenced the writers in their use of this material in treating cancer of the cervix are these:

1. After activation in a nuclear reactor,‡ cobalt-60 has a half life of 5.3 years, making it relatively stable.
2. It has a soft beta radiation which is easily filtered out.
3. The gamma radiation is homogenous—1.16 and 1.31 Mev.
4. The strength of any given lot of the material is determinable prior to irradiation in the pile. Two pieces of cobalt of identical weight and size when exposed to the reactor for different lengths of time will have different intensities when activated, and such values can be calculated ahead of time.
5. Residual activity can be "warmed up" in the reactor.
6. There are no gaseous radioactive daughters, leakage is impossible, and the regrouping of units of activity is facilitated.
7. After activation cobalt remains magnetic, which also facilitates handling. A long rod with a controllable magnet at the end is used for transferring the material and for loading the needles. This provides additional safety for those who handle the radioactive material.
8. Cobalt-60 can be activated in any desired shape and form, and in any desired quantity at a moderate cost.
9. Suitable alloys can be found which are chemically inert, inexpensive, and easily machined. The alloying material can be so selected that it is not necessarily activated by the nuclear reactor.

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†Read by invitation, at the Seventy-Third Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 11 to 13, 1950.

‡The material used in this study was activated in the Oak Ridge Nuclear Reactor (Pile).

Considering these properties, it will be noted that many of them (Nos. 6 to 9) contribute predominantly to making the material one that can be safely and easily handled. Whereas radium units must be regrouped with precautions against gaseous emanations and with some difficulty, expense, and loss of time, cobalt represents a material which can be made available in varying strengths and easily handled shapes. The soft beta ray reduces the amount of shielding necessary, and the regrouping of cobalt can be effected in thin-walled, slender needles rather than in capsules or thick needles. Accordingly, the thesis of our clinical application of radioactive cobalt to the problem of cervical carcinoma has been to take advantage of these properties and to regroup and rearrange liberally the individual sources of radioactivity so that the resulting combination provides a field of intrapelvic irradiation adjusted to the particular patient being treated.

The objective of this therapy, quite obviously, is to provide a tissue roentgen dose to the pelvis so distributed that the uninvolved viscera will have maximum protection while the malignancy receives adequate irradiation as its nature and direction of spread might demand. The program which has been designed to achieve this objective is based primarily on careful patient individualization and study. This has involved not only clinical evaluation of the extent and classification of the neoplasm, but also a series of roentgen studies and pelvic mansurations previously described.³ Once such measurements have been completed, the direct therapy has resolved itself into designing individual applicators for each patient, and inserting them for a six- to seven-day period to provide approximately a 6,000 to 7,000 tissue roentgen dose to the neoplasm. To achieve such individual application, three agents are employed:

1. *Needles.*—Irradiation therapy of the pelvis by means of needles has its opponents⁴ as well as its supporters.^{5, 6} Needle therapy, however, allows low intensity, multisource irradiation to large volumes, reducing "hot spots" and resulting in more homogeneous dosage. The potential advantage it represented in this particular form of treatment was that it permitted individual grouping of the cobalt-60 cylinders within each needle, as well as varied arrangements of the needles within the pelvis. With our source of cobalt-60, fine aluminum needles of 1.27 mm. total diameter can be employed and as many as 36 needles have been used in a single applicator, with the result that each individual source of irradiation can be mild, and its individual "hot spot" of immediate effect minimal.

Preliminary studies included the implantation of activated cobalt needles in dogs to provide absurdly large doses of radiation to the pelvic viscera—particularly the bowel, bladder, and ureter—and the placing of inactive, dummy needles in patients scheduled for gynecologic surgery for nonmalignant lesions to permit direct visualization at operation of the precise location of the needle tips in relation to the pelvic structures. Furthermore, twelve patients who had implantations for therapeutic purposes have had under the same anesthesia exploratory laparotomies to determine needle placement. From these studies, as well as from our clinical experience with the patients treated to date, we have reached the conviction that there is little danger of visceral or vascular injury inherent in this form of therapy, provided the patient is carefully studied pre-operatively and the needle pattern predetermined with reference both to the

distribution of the malignancy, the location of the bowel and bladder, the size of the pelvis, and other individual variations.

2. *Templates*.—One of the difficulties inherent in the needle technique of irradiation lies in the deviation of the needle from its desired pathway in the process of insertion. The effect of such deviation is stressed in Fig. 1, which shows that a deflection of 12° in needle position decreases by 53 per cent the irradiation intended for point X.

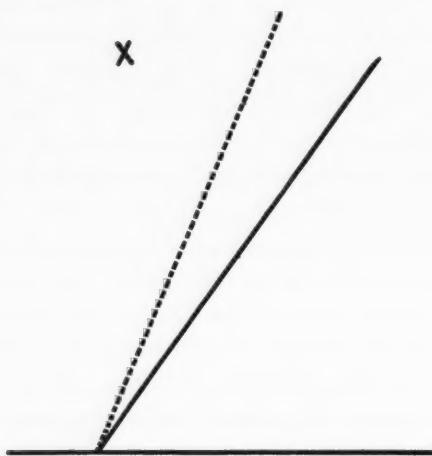


Fig. 1.—The interstitial needle was intended for the position indicated by the dotted line. It was actually placed on the solid line. Such a small deviation (approximately 12°) results in a diminution of 58% in the amount of irradiation intended for area "x."

To reduce this meandering of the needles to a minimum, a series of plastic plates have been employed, each containing holes drilled for the needles. The plates are 0.25 to 0.5 inches thick, and the placement and precise angulation of each needle are predetermined by the hole designed for it.

Using such a series of templates, it is possible to assemble the entire unit of needles prior to placing them in the patient and to measure the amount of irradiation which will be received per hour at various points. Fig. 2 shows such an assembled unit, and the anteroposterior and lateral pelvic x-rays of a patient under therapy are shown in Figs. 3 and 4. These x-rays indicate, as have all those taken on patients being irradiated with cobalt, the smooth symmetrical placement of the needles using the templates as needle guides.

3. *Cobalt*.—In these studies we have used cobalt both as the nickle-cobalt alloy, cobanite, and as the pure cobalt metal. In the latter form it is submitted for activation as 0.3 cm. lengths of 0.508 mm. diameter wire. After activation these cylinders are placed in the needles using inert aluminum cylinders between to distribute the linear intensity as desired. The length as well as the strength of each needle can in this way be adjusted for its particular location (Fig. 5).

Procedure

As an initial step in their therapy, the patients have received external x-irradiation (2,000 r to a 20 cm. by 20 cm. anterior port and the same dose to a similar posterior port). The measurements which determine the size of the templates and the arrangement of the needles are made toward the close of this series of treatments.

After the plates and needles have been prepared, they are sterilized and the insertion carried out under Pentothal anesthesia. The first plate can have

a small rod projecting from its surface and designed to fit into the cervical canal, or it simply may be held in place while the individual needles are inserted through the appropriate holes prepared for them. Each subsequent plate then fits on the preceding one, thus automatically positioning the whole group. The needles continue to be inserted one at a time through the holes

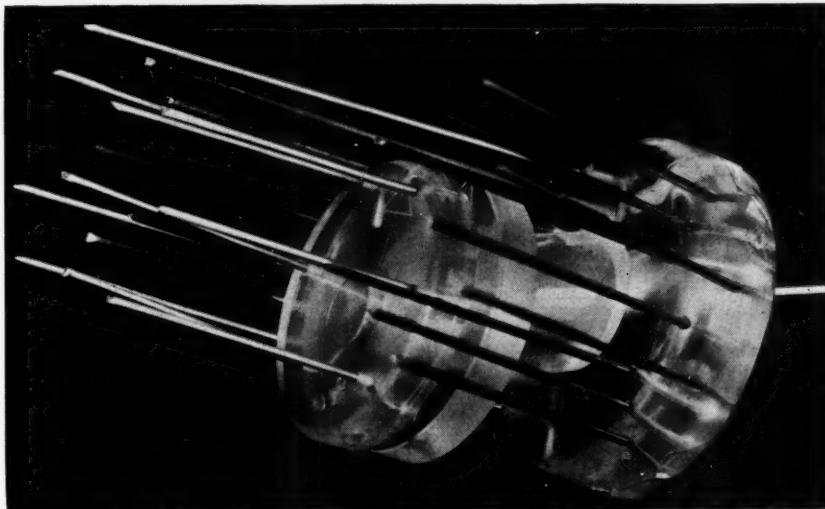


Fig. 2.—A sequence of templates assembled with its needles. In this application the cervical needles are placed through the holes in the first plate. The paracervical and wide parametrial needles through the large plate at the base.

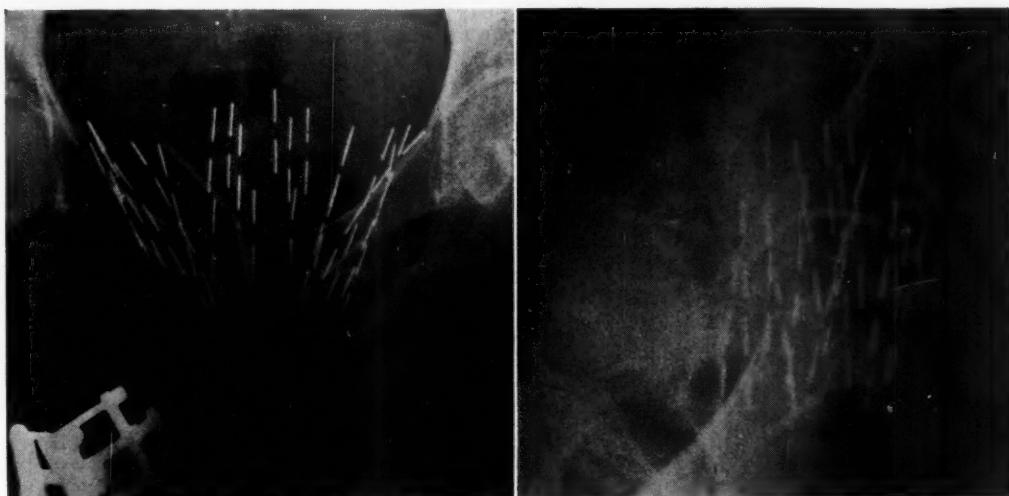


Fig. 3.

Fig. 4.

Fig. 3.—Anteroposterior film of a patient with needles in place. The needles here, as well as the slugs between the cobalt cylinders, are aluminum, so that only the cobalt itself shows on the x-ray.

Fig. 4.—Lateral view of a patient under therapy. The even symmetrical placement of the needles is indicated by these films.

designed for them until the unit is complete. In general the first plate carries the cervical needles, the second the paracervical and the third the wide parametrial. The basic needle pattern used is a modification of that suggested

by Corscaden,⁵ but variations of this pattern are frequent, since individualization remains one of our chief objectives. Fig. 6, for example, reveals the distribution of needles designed to reach a postsurgical recurrence lying at the right vaginal apex and almost completely surrounded by bowel and bladder.



Fig. 5.—To increase the linear dose per needle locally, the cervical needles have been loaded without inert slugs between the cobalt. The parametrial needles have spacers between the active slugs.

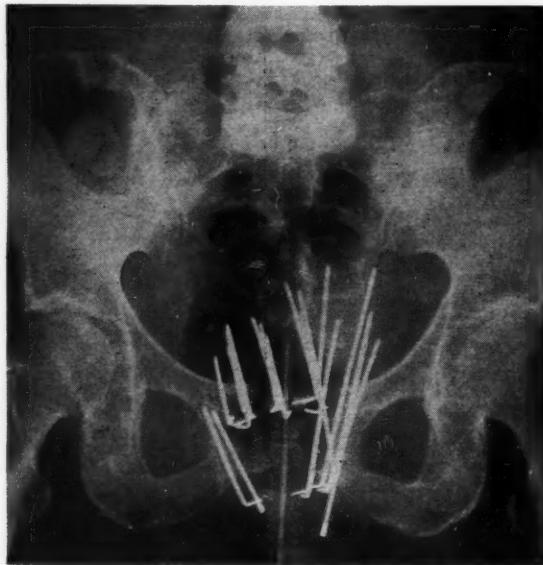


Fig. 6.—Needles (fine steel) carrying cobalt to a postsurgical recurrence at the right of the vaginal apex. Only the distal ends of the needles are active.

After insertion the entire mass of templates and needles is packed in place and usually remains for six to seven days. X-rays of the pelvis have indicated that the needles do not move during this time, and the objective is to

administer a dosage in the neighborhood of 6,000 to 7,000 tissue roentgens to the tumor with moderate intensity over a long period rather than in a more intense dose over a briefer time.

Results

It is, of course, impossible to discuss results in terms of a five-year survivor rate. The first application of Co-60 to carcinoma of the human cervix was made in October of 1948, and, moving cautiously to observe the reactions of each patient during the early months, a total of only forty patients have been treated to date. Five-year survival figures are going to be of little help, furthermore, since the first patients selected for cobalt therapy were already hopeless cases, and all the patients collectively do not constitute a promising group for therapeutic success.

By League of Nations Classification, one patient was in clinical Class I, fifteen were in clinical Class II; sixteen were in clinical Class III and six patients in clinical Class IV when treated. The remaining two women had carcinoma of the cervical stump. From the point of view of the previous treatment status, five patients had had ineffective treatment, and their condition was considered hopeless when cobalt therapy was carried out. An additional five had received previous therapy which was felt not to be acceptable as adequate treatment by the Gynecologic Carcinoma Conference which considered these patients. The remaining thirty women had precobalt therapy which was adequate in dosage and which was administered without undue loss of time.

It is well to remember with respect to these gloomy statistics, however, that the present place of radium in the treatment of cervical carcinoma was not decided on the basis of the results in the first forty patients who may have received radium therapy. Actually, the fact to be determined from the present status of these patients is whether or not any unique harm or disability accrues from treatment with cobalt-60, and whether or not the technique justifies further study.

Early in the evolution of this program, when approximately sixteen needles were being used to carry the total dose, and when the therapy was accomplished in five days, there was a definite incidence of bowel morbidity in the form of diarrhea and tenesmus which may bode ill for these patients in the future. As the number of needles has increased, however, reducing the dose per needle, and the period of therapy has been lengthened to seven days, and as we have also angled the needles further forward in the pelvis, the severity and incidence of the bowel reactions have tended to subside.

While the patient is under treatment, an indwelling catheter is left in place, and bladder morbidity in the form of dysuria, tenesmus, or cystitis has been rare. One vesicovaginal fistula has occurred (10 months post therapy) in a patient (clinical Class IV) who had had a bladder papilloma visualized preoperatively. Examination at present indicates that the bladder floor is extensively infiltrated, and the fistula is neoplastic rather than radiologic in nature.

In their systemic reactions, these patients have been no more febrile and no more toxic than patients receiving a corresponding tissue roentgen dose of radium.⁷ It is imperative to remember, however, that all dosages must be calculated and all comparisons must be made in terms of tissue roentgens. A millicurie of cobalt-60 produces more gamma roentgens per unit time than does a millicurie of radium under the identical conditions (in the ratio of 11.5 to 8.4), and dosages figured in millicuries or millicurie hours are an unsuitable form of calculation.

Three patients of this group died within a few weeks of completing their cobalt therapy. One had an already hopeless status and her downhill course was seemingly neither slowed nor speeded by treatment with Co-60. The second was a 68-year-old hypertensive, arteriosclerotic woman who apparently experienced a coronary occlusion. The third patient had had a positive biopsy from the supraclavicular region and x-ray evidences of lung invasion; her death (outside the hospital) was described as being pulmonary in nature. Five additional patients have died at times between five and eleven months after treatment, and post-mortems are available on four of these. The findings in these women range from pelvic cancer which appears almost untreated on the one hand, to a relative absence of actively growing neoplasm on the other; a range which is characteristic of patients who have been treated with more traditional forms of irradiation. One of these four died in uremia; three from cachexia and generalized carcinomatosis.

The possibility of remote disabilities to the surviving patients arising from this form of therapy cannot, of course, be ruled out. It would seem unlikely, however, that this particular isotope should display unique human effects not predictable from the animal investigation. To date, we have found nothing inherent in the patient reaction to radioactive cobalt itself to cause us to abandon the present investigation. Using a special adapter on the Geiger counter, counts have been made from the interior of the bladder, the rectum, and from within the peritoneal cavity at laparotomy on patients who are under therapy. These counts indicate that the field of irradiation is satisfactory, and the technique achieves the desired distribution of effect with precision.

Summary

After activation in the nuclear reactor, cobalt forms a relatively stable isotope with a soft beta ray which requires minimal shielding, and has a homogenous gamma irradiation. It can be machined to any desired shape prior to activation, and constitutes an easily handled radioactive material. Advantage has been taken of these qualities in the application of cobalt-60 to the treatment of the forty patients with carcinoma of the cervix here reported. Fine caliber needles have been used which can be fashioned to the desired length and strength, and template guides have been introduced to provide precision of needle placement. These factors tend to increase the safety of multiple-source intrapelvic irradiation, and a method is offered whereby an evenly distributed pattern of radiation can be designed to fit the patient's pelvis and the spread of her lesion.

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Discussion

DR. CHARLES A. BEHNEY, Los Alamos, N. M.—Artificially produced radioactive isotopes of the various elements have been employed widely as isotopic tracers, but there has

been little exploitation of them for the treatment of malignant diseases. When used for this purpose, the results have been, on the whole, disappointing. We are indebted to Dr. Barnes for his report. It demonstrates the superiority of an inexpensive, easily handled material as compared with radium, for the treatment of carcinoma. The gamma rays emitted by cobalt-60 are capable of penetration equivalent to that of the rays of a million volt x-ray machine, from which all soft rays have been filtered. His ingeniously devised templates are a valuable addition for precise positioning of the needles.

Taylor and Twombly have demonstrated the increased morbidity following interstitial irradiation, over radium application by contact. Waterman reported a mortality of 1.2 per cent with his interstitial technique, all deaths having resulted from sepsis. In the same series he, however, achieved a 5-year salvage of 100 per cent in Stage I, 68 per cent in Stage II, and 30 per cent in Stage III cases. Such good results perhaps justify the slightly increased hazard by this method from infection and necrosis. In both the above series, furthermore, the large needles needed for radon seeds were used and their positioning was admittedly less accurate than that demonstrated by Dr. Barnes in his slides. We have had presented to us today a refinement of the Corscaden principle of uniform distribution of point sources of radiations. This, in addition to the superior quality of the rays from radioactive cobalt should assure the improved end results anticipated, which, however, only further use of this method and time can prove.

Additional experience will undoubtedly lead to technical improvements. According to the inverse square law, the intensity of the dosage immediately adjacent to the needles when they are situated 1 cm. apart is approximately eight times as great as the dose midway between them. It is desirable to minimize this discrepancy. Preliminary high voltage x-ray therapy as used by the author reduces the infectious potentialities of the pelvic tissues. The tendency to infect the deeper pelvis structures by interstitial irradiation may be capable of further modification by the use of antibiotics before insertion of the needles and during their sojourn in the tissues.

Dr. Barnes is to be complimented on the ingenuity displayed in formulating his technique. His presentation is of further importance in that it calls attention to the value of radioactive isotopes in the treatment of pelvic carcinoma, and because he has introduced a more efficient, readily available, and comparatively cheap substitute for radium.

DR. WILLIAM HEALY, New York, N. Y.—I am sure that everyone here has been most favorably impressed by this splendid communication of Dr. Barnes. In discussing the paper I want only to bring out one point which I think is extremely important in the use of interstitial irradiation for carcinoma in any part of the body, and that is the preliminary roentgen therapy before puncturing the carcinomatous tissues with a foreign body. That puncture could very readily spread carcinoma cells into the lymphatics and blood vessels. I think it is highly important before this is done that the carcinoma cells be reduced in their viability by preliminary irradiation which, of course, is best given by means of the roentgen ray. For many years at Memorial Hospital in the treatment of cervical carcinoma we have adhered to the preliminary use of roentgen therapy before using radium.

DR. BARNS (Closing).—These patients do receive external x-ray therapy prior to insertion of the cobalt and our motive is the dual purpose of preventing potential spread and aiding us in the control of sepsis. We have had no sepsis. The patients are started on antibiotics the day before therapy and they receive penicillin daily during treatment. They have been somewhat febrile in their reaction but slightly less febrile, on the average, than have patients receiving radium in the cervix and fornices. The latter are often febrile presumably due to the central necrosis which occurs based on the inverse square rule that Dr. Behney mentioned.

Both of these comments revolve around technique and I should like to discuss that aspect briefly. I am not advocating any particular technique. We were the first to use cobalt in human beings and it seemed to me then, as it does now, that if we ground it up into a fine powder, poured the radium out of the capsules and large needles, poured ground cobalt in

and used it entirely as a radium substitute, we would have failed in our responsibility. We were obligated, it seemed to us, to make an effort to take advantage of the characteristics of the material and not just to use it as a substitute for radium. Whatever else may be said of this technique, it must be admitted that it does make that effort to take advantage of the properties peculiar to Co-60. In other words, we have tried to translate the characteristics of the material into advantages. This is the first technique by which cobalt has been used, and I am not innocent enough to believe that the first technique devised will also be the final technique. If this represents a step, then one would hope that other steps would be taken and other modifications in procedure made, because we must take advantage of the characteristics of each of these isotopes if we are to provide complete therapy for our carcinoma patients.

A METHOD OF DIAGNOSING AND TREATING FUNCTIONAL PELVIC DISEASE*

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INTEREST in the problem of functional pelvic disease has increased in recent years. It is recognized that any of the symptoms which usually result from organic disease may appear as a result of emotional and psychological disturbances. Every disease has a somatic and a psychic component. Fordyce Barker,¹ in his presidential address before the Second Annual Meeting of the American Gynecological Society, discussed the frequency with which the correction of emotional problems relieved symptoms in patients with apparent organic pelvic disease. He also urged a revival of conservative management in gynecologic treatment. Cooke² has stated, "Ninety-five per cent of the severity of human suffering is mental; a great deal of the symptomatology encountered in the practice of gynecies is of purely mental origin." The recent gynecologic literature contains an increasing number of references to the psychosomatic origin of some specific gynecologic complaints.^{3, 4, 5} The use of hypnotism and suggestion in the treatment of obstetric and gynecologic diseases is receiving attention.^{6, 7, 8}

In the majority of our patients predominance of the somatic or the psychic factor in a patient's illness is obvious, and little difficulty is encountered in making a diagnosis. However, in a large group of patients the psychic and somatic conditions overlap, making accurate differentiation extremely difficult.

A previous study⁹ of the private gynecologic patients referred to our clinic revealed that 32.5 per cent of them suffered primarily from functional disease. Thirteen per cent of the patients had pathologic changes in the pelvis in addition to a functional complaint. Many patients were referred for various operative procedures which were unnecessary after a fundamental emotional problem had been solved. Others had a pathologic lesion treated elsewhere, but had failed to respond because an unsolved psychological problem was present.

The purpose of this paper is to evaluate the methods we use for diagnosing and treating functional pelvic disease. Such an evaluation must be based upon the accuracy of the diagnosis, and the patient's response to treatment. A summary of the results obtained in the treatment of this series of patients is therefore included in the data.

Methods of Diagnosis and Therapy

An important factor in the diagnosis of functional pelvic disease is the establishment of a satisfactory personal patient-physician relationship. The method which we have used is as follows:

In a preliminary interview, the physician obtains a complete medical history. No abbreviated record forms are used and no preliminary history is

*Presented, by invitation, at the Seventy-Third Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 11 to 13, 1950.

taken by the nurse, secretary, or assistant. The gynecologist performs a complete physical examination in which the pelvic examination invariably comes last.

When no organic disease is found, or when a gross pathologic lesion is not sufficient to explain the patient's complaints, the further diagnostic studies and consultations which are indicated are obtained. The purpose of these is to rule out, so far as possible, obscure diseases as a cause of the patient's symptoms.

A frank appraisal of the problem is then presented to the patient. Her confidence is gained by the physician's acknowledgment of the reality of her symptoms. Her cooperation is usually obtained by a simple explanation of the mechanism responsible for the production of pain in functional disease. She is advised that severe pain and other symptoms may often result from vascular spasm or other involuntary contractions of smooth muscle. She is told further that these changes frequently result from fear or worry about some situation which may arise in the daily life of anyone. The spastic colon and gastric ulcer are cited as examples of organic lesions which are generally thought to be the result of tension states.

A patient who is incapable of accepting a diagnosis of psychoneurosis may be pleased at the explanation that her symptoms result from failure of the organs "to work properly." This may free her of the illusion that an infection, neoplasm, or birth injury is present.

When pelvic disease is present, its exact character and the consequences of conservative or operative treatment are fully explained. Many women are under the impression that the entire bowel may suddenly fall out or that a cancer may develop if an asymptomatic rectocele of moderate size is not repaired. The reassurance which results from an understanding of the true possibilities may relieve a multitude of symptoms.

The relative seriousness of an emotional problem bears little relation to its significance as a cause of functional complaints. If a condition which is unacceptable to the patient cannot be changed, she must make adjustments in her attitude which permit her to accept the problem. Otherwise, chronic tension is certain to occur.

Many patients recognize their own problem immediately when this information has been given to them. They may volunteer the details of a situation which is a source of worry or tension, and ask for advice. Others may obtain insight, and, without giving the details, express confidence that they can overcome their difficulties since they understand the cause of their symptoms. Equally good results are obtained in these two groups of patients. A patient with a profound fear of cancer may require repeated reassurance, and many unnecessary laboratory examinations may be required to console some of these patients.

Even when it is evident that the patient will not accept a diagnosis of functional pelvic disease, the physician should give his diagnosis with confidence. Consultation and further study in the hospital to confirm the clinical impression should be offered. Studies should be carefully selected in order to rule out disease processes which might cause the patient's symptom complex. It is not necessary to make an elaborate study of all major systems in an effort to prove complete physical normalcy in the patient.

Psychiatric assistance is suggested for every patient who does not promptly recognize the emotional problem that is responsible for her illness, or refuses to admit to such a problem even though it is evident. We do not believe that a gynecologist should attempt to analyze a patient or to undertake any form of professional psychiatric treatment. He may, however, allay fear and offer advice based on sound common sense, with excellent results.

Analysis of 2,315 Cases

The 2,315 patients in the series were all private office patients of one of us (F. R. L.), and all were of the white race. The only patients in the series who were not referred directly for office consultation were the wives of physicians and personnel of the medical school and hospital.

Three major groups of patients were recognized:

1. Those who presented sufficient pathologic findings to account for their symptoms—1,709 patients (73.7 per cent).
2. Those whose symptoms were too severe to be accounted for by the physical findings—397 patients (17.2 per cent).
3. Those with numerous symptoms in whom no pathologic lesion could be demonstrated—209 patients (9.1 per cent).

A total percentage of patients in Groups 2 and 3 (26.3 per cent) represents the incidence of functional pelvic disease in this series.

Group 1.—

Table I shows the major diagnoses which were made on the 1,709 patients in Group 1. Two hundred sixteen patients in this group had apparent gynecologic symptoms due to diseases of other systems.

TABLE I. DIAGNOSES MADE IN GROUP I

	NO. CASES
Pregnancy and complications	497
Endocrinopathies (including sterility, dysmenorrhea, etc.)	344
Infection	201
Benign tumors	182
Relaxations, malpositions, and lacerations	139
Malignant growths	65
Endometriosis	50
Congenital anomalies	15
Diseases of other systems	216

Group 2.—

Tables II and III list the major organic diagnoses and the psychiatric classifications of the 397 patients in Group 2. Each patient in this group has both an organic and a psychiatric diagnosis.

TABLE II. ORGANIC DISEASE FOUND IN GROUP 2

	NO. CASES
Pregnancy and complications	20
Endocrinopathies	49
Infection	71
Benign tumors	91
Relaxations, malpositions, and lacerations	152
Malignant growths	0
Endometriosis	4
Congenital anomalies	3
Diseases of other systems	27

TABLE III. PSYCHIATRIC DIAGNOSES MADE IN GROUP 2

	NO. CASES
Anxiety	128
Phobia	95
Adult maladjustment	69
Psychoneurosis	35
Miscellaneous	70

One hundred thirty-four of these patients required special diagnostic studies in addition to the complete history, physical examination, complete blood count, analysis of a catheterized specimen of urine, and blood Wassermann test, which are routine procedures. Table IV lists the number of patients subjected to various types of special study. All types of roentgen studies are included under this heading and, in most instances, more than one roentgen examination was made. Metabolic studies include basal metabolism determinations, glucose tolerance tests, and similar procedures. Fifty-three consultations with other specialists were obtained. Eleven patients required cystoscopic examination, and 43 were admitted to the hospital for a part of their examination, including 27 for whom dilatation and curettage were required.

TABLE IV. SPECIAL DIAGNOSTIC PROCEDURES NECESSARY IN GROUP 2

	NO. CASES
Roentgen studies	30
Dilatation and curettage	27
Metabolic study	24
Consultations	53
Cystoscopic examination done by urologist	11

In the vast majority of these patients, simple emotional problems were present which required little expert treatment. Fear of cancer and of major operations was commonly observed. Anxiety concerning the probable progressive character of the pelvic disease was an outstanding factor in many cases. Psychiatric care was recommended for 17 patients in this group (Table V); 16 accepted this recommendation. Four of these 17 patients were referred by a psychiatrist for evaluation of the condition of the pelvis.

TABLE V. PSYCHIATRIC CARE OF PATIENTS IN GROUP 2

	NO. CASES
Psychiatric consultation recommended	17
Consultation accepted	16
Consultation rejected	1
Referred by a psychiatrist	4

The operative treatment of gynecologic lesions was determined by a policy which weighed the risk of conservatism against that of radical treatment. The risk of operation is probably greater than the danger of conservatism to the life and health of the patient with uterine fibroids, inflammatory cystic disease of the tubes or ovaries, malpositions, relaxations, or comparable lesions. However, surgical intervention may be necessary when the symptoms resulting directly from the pelvic lesion are severe. The usual office procedures were used to correct minor lesions.

TABLE VI. RESULTS IN GROUP 2

	NO. CASES
<i>Period of Follow-Up.—</i>	
Less than 6 months	50
6 months to 1 year	35
1 year to 3 years	74
More than 3 years	36
<i>Results in 195 Cases Followed.—</i>	
Relieved of symptoms and organic disease	58
Relieved of symptoms without cure of organic disease	108
No relief or incomplete relief	29
	85 %
	15 %

Of the 397 patients in Group 2, only 195 could be followed long enough to determine the result of treatment. It was gratifying to learn that 166 (85 per cent) of these had been completely relieved of all symptoms. In 58 the organic lesion had healed and the symptoms resulting from functional disease had disappeared. One hundred eight patients had no complaints in spite of the fact that pelvic pathologic conditions were still present. In 29 patients symptoms had persisted although some of them were improved.

The two case reports which follow illustrate the excellent result which may be obtained by proper treatment of a functional problem, and the poor result which may follow satisfactory management of an organic lesion if a serious functional component of the illness is overlooked.

CASE 1.—A divorcee, 28 years of age, entered the hospital for evaluation of the status of an old syphilitic infection. Her complaints included dysmenorrhea, lower abdominal pain, and leucorrhea. Menstruation was normal. Gonococcal infections had been proved on three occasions, and three surgeons had advised a major abdominal operation.

Examination revealed a Bartholin's gland cyst, chronic endocervicitis, and chronic bilateral tuboovarian disease. The cystic mass in the left adnexa measured 8 cm. in diameter, and that in the right adnexa was 5 cm. in diameter. All of the pelvic organs were fixed, but only moderate tenderness was present. Cultures were negative.

When the problem was explained to the patient, it was learned that she had an intense fear of operation because she believed that it would destroy sexual function. In view of a definite diagnosis of old pelvic inflammatory disease, conservatism was suggested. All pelvic symptoms disappeared in one month.

The patient had been free of symptoms for four years when she was last examined. The cystic masses in the adnexa measured 10 cm. and 7 cm. in diameter. She had remarried and was leading a happy and useful life.

CASE 2.—A housewife, 34 years of age, complained of dysmenorrhea, pelvic pressure, prolapse, and infertility. She had been pregnant twice, fourteen and eight years prior to consultation. The first child weighed 9 pounds and was lost in a difficult instrumental delivery. The second was lost because of prematurity. A suspension operation performed seven years prior to consultation had not brought about any improvement.

Examination showed a large urethrocele and cystocele, with prolapse of the bladder and of the cervix through the introitus, and moderate relaxation of the posterior vaginal wall.

No history suggesting psychiatric disease was obtained. The patient was fitted with a Hodge type pessary in the hope that this would provide symptomatic relief and that mechanical correction of the organic lesion would result in pregnancy. One year later the patient decided to have an operative repair and a Manchester procedure to correct the prolapse. Postoperatively she demanded large quantities of narcotic and hypnotic drugs. Drug addiction was suspected and a psychiatric consultation was obtained, but the advice of the psychiatrist was rejected by the patient. Her cooperation with the psychiatrist was poor, and no exact diagnosis resulted from his interview.

After fifteen months the patient was seen again. She was in the twelfth week of pregnancy and was suffering from severe malnutrition. A fall had resulted in a fracture of the clavicle, and fibrous healing was present in spite of an open reduction. At the twenty-seventh week of pregnancy the patient had nutritional edema (total serum proteins 4.6 Gm. per 100 c.c.), anemia (hemoglobin 10.0 Gm., red blood cell count 3,500,000), and mild hypertension without albuminuria. She entered the hospital at the insistence of her physician and her husband. In addition to diet, sedation, and rest, protein hydrolysate was given on one occasion as a device to keep the patient in the hospital. All consultations were rejected by the patient, and she left the hospital against advice after three days. Three weeks later she was admitted to her local hospital, where blood transfusions were given in addition to further infusions of protein hydrolysate. Following the second in-

fusion she had a severe reaction with circulatory collapse. Intrapartum death of the fetus occurred during this incident, but labor did not ensue. The patient's course was downhill as a result of the excessive use of drugs. It was learned that she died from burns sustained when her clothing accidentally caught fire in her home.

Group 3.—

Two hundred nine patients were seen who had symptoms of pelvic disease without any demonstrable organic lesion. The psychiatric diagnoses made in this group of patients are given in Table VII. As one would expect, a greater variety of emotional problems and more serious psychiatric diseases were encountered in this group.

TABLE VII. PSYCHIATRIC DIAGNOSES MADE IN GROUP 3

	NO. CASES
Psychoneurosis	65
Adult maladjustment	61
Psychosis	24
Anxiety	22
Phobia	12
Pruritus	8
Hysteria	3
Miscellaneous	14

The number of patients subjected to various supplementary diagnostic procedures is given in Table VIII. Psychiatric care was recommended for 55 patients (Table IX), and accepted by 45. It is our policy to recommend psychiatric consultation only after we believe the patient will accept this advice. In many instances the condition may be made worse and resentment reactions created by a premature recommendation of psychiatric care. Often a simple fundamental problem can be solved easily by sound advice, so that no further treatment is required.

TABLE VIII. SPECIAL DIAGNOSTIC PROCEDURES NECESSARY IN GROUP 3

	NO. CASES
Roentgen studies	26
Dilatation and curettage	2
Metabolic study	9
Consultations	36
Cystoscopic examination done by urologist	7

TABLE IX. PSYCHIATRIC CARE OF PATIENTS IN GROUP 3

	NO. CASES
Psychiatric consultation recommended	55
Consultation accepted	45
Consultation rejected	10
Referred by a psychiatrist	14

TABLE X. RESULTS IN GROUP 3

	NO. CASES
<i>Period of Follow-Up.—</i>	
Less than 6 months	49
6 months to 1 year	8
1 year to 3 years	17
More than 3 years	12
<i>Results in 86 Cases.—</i>	
Well	46—53%
Improved	16—19%
No relief	24—28%

The results of treatment in this group of patients (Table X) were less satisfactory, since the basic emotional problem was frequently more serious and deep-seated. Some patients do well under professional psychiatric treatment; others cannot be persuaded to obtain psychiatric help, and wander from one doctor to another, seeking relief from their complaints.

The two cases which follow illustrate an excellent result obtained with simple psychotherapy and an extremely difficult problem of management.

CASE 3.—The following is an exact transcript of a written statement the patient brought to me at the time of consultation:

"Mrs. _____, born May 7, 1914. Menstruation began at age of 13. Periods regular, 28 to 30 days. Quite a bit of pain in back and lower part of abdomen. Flow very small lasting 3 to 4 days. This continued until pregnancy in Dec. 1938 at age of 24. Had quite a bit of trouble during childbirth. Weight 198½. Before pregnancy weight —145. 5 weeks after birth of child had pyelitis. 5 weeks later became pregnant. Mis-carriage at 2 months pregnancy. When menstruation began had very little pain, only dull headache. Flow lasting 1 to 2 days. Very small. In 1940-41 treated for overactive thyroid. Periods lasting ½ to 1 day. Very nervous. B-M-R plus 40 in first test. Later plus 20. After taking Lugol, Oct. 1941 to Jan. 1942 much improved. Dieted (under Dr.'s prescription) Weight 118—became very ill and nervous in March, 1942 and Dr. _____, Charlotte removed exophthalmic goitre—1942-43 nerves were much improved. 1944 nervousness increased. Had spells of pain in back, stomach and abdomen. A white discharge Dr. _____, New Bern made exam—found nothing wrong. Special compound for douching. Left eye became infected in March, 1944. Drs. could find no cause. All said, focal infection. Sinuses and teeth were all right. This cleared somewhat after using drops in nose. Had exam by Dr. _____. Said thyroid was fine. Needed a tonic. I still had severe pains in abdomen and back, and food did not digest very well. In June 1945, I had, what I thought, was acute appendicitis. Abdomen and stomach seemed tied in knots. Dr. _____ of Kinston prescribed Atabrine—1 a day as long as I was on the coast. (I was 30 miles from Morehead City.) This I did for two months. I seemed much worse then before. Dr. _____ of New Bern, said take no more atabrine and gave me Lextron Ferrous. I soon felt better. In May 1946 headaches and a grating sensation in back of head. These were 2 to 3 times a week. Heat made this much worse. My nerves were no better. Had hemogl. test. This was 50—more Lextron Ferrous. Entered hospital, Greensboro—Dr. _____ made ex-rays of entire head. Found 2 spots, Dr. _____, Richmond said were calcium formations. Grating sound was caused by ruptured disk in cervical spine. Advised leaving coast. This was August 1946. Dr. _____ then gave me nicoteric acid shots and tablets. The tablets I took for 2 month. Sept. 1946 we moved to N. Wilkesboro. Much improved until last of Nov. Knots again in abdomen and digestion bad. Menstruation began 4th of Dec. lasting a few minutes normal then black, stringy discharge. No more pain then usual. Mostly in right side. Dull headache. This lasted 5 days. Then severe pains in right side. Dr. _____ made exam. Could be pregnant. Womb enlarged. Only symptom. Needed appendectomy and cyst removed from right ovary. In bed 5 days discharge continued. Then severe pain in back and abdomen every 3 to 5 minutes, as tho in labor. Entered N. W. hospital. Had shots in hips for 4 days. Discharge stopped. 12 hours later began. I had sulpha drug. 12 hours of bad hip leg and back pain. To urinate very painful. Chalky and thick. Discharge continued till Dec. 30. Stopped. Mens. started January 2nd 1947. Same as Dec. 4th I did nothing—only stay in bed. Cleared completely Jan. 8th. Dr. _____ made exam. Jan. 14th. Definitely not preg. Entered Piedmont Memorial Hospital, Greensboro Jan. 20th—During exam. found lipomas in back. Ex-rays made of entire body. Found injury on spine. 3rd vertebra lumbar—Jan 24th had D&C. Found very little trouble there. Pains continued from naval to pelvis. As tho a string was drawn tight. Had B. M. R. Feb. 3rd—plus 22. Another on Feb. 12th—minus 16. Feb. 14 Dr. _____ removed appendix and cyst from left ovary. Feb. 22 removed lipomas 1 very large on left side and several small ones on right. Returned home

March 7. Menstruation began March 12. 2 days normal, then black discharge for 3 days. Pains as before, lasting 12 or 14 hours. A week later I discovered more epis. lipomas. April 8 menst. lasted 2 hrs. Mostly black. Same pain as before. May 6th same as April. June 12th (38 days) very severe pains and taking "pain" medicine prescribed by Dr. _____. Said womb was enlarged. June 19th Dr. _____ made exam. advising to go back to operating Dr. June 21st Dr. _____ made exam. Red blood cells in urine. Possibly stone. Womb not enlarged. To return to hospital next menst. period (gave no medicine) Dr. _____ made urinalysis June 25th. Nothing was wrong. Advised my seeing Dr. _____. Gave me ovarian tablets. Mens. began July 10 (29 days) flow lasting 4 to 5 hours—small—light red. Then white discharge for several days. No pain, except for headache. Am taking the tablets as of this date. August 1, 1947."

The physical findings were: mild obesity; the scar of a recent low right rectus incision; tenderness over the lower abdomen; a recent red, very tender scar on the back in the region of the left sacroiliac joint; mild relaxation of the pelvic outlet; slight cystocele and rectocele; and fixation of both ovaries to the broad ligaments and adjacent structures, with marked tenderness.

The patient entered the hospital and remained four days. A surgical consultant reassured her about the scar on her back and the danger of malignancy in association with lipomas. Routine laboratory studies were normal. Special studies included a basal metabolism test (-9), serum cholesterol determination (202 mg. per 100 c.c.), blood bromide level (40 mg. per 100 c.c.), and a glucose tolerance test which was normal. No roentgen studies were made.

The patient was advised that no significant organic disease was present, and that she must have some emotional problem which was responsible for her complaints. She quickly stated that she had an abnormal concern about the health and welfare of her one child. After she was advised concerning this problem, she left the hospital to follow a reduction diet.

She was relieved of all of her symptoms within two weeks, and her menstrual cycle subsequently became normal. The patient has been followed for two and one-half years. She has remained completely well, and returns for reassurance at intervals of six months.

CASE 4.—The patient was 30 years of age and had been married six years. During four years of their marriage she and her husband had been separated as a result of the husband's military assignment. No contraceptives had been used for ten months prior to consultation.

The patient complained of intense lower abdominal pain which was constant and was increasing in intensity. She had had oligomenorrhea with spotting at irregular intervals for five months. For one week the pain had been severe enough to require the frequent use of narcotics. A laparotomy had been recommended.

Examination revealed no detectable abnormality. The patient complained bitterly of tenderness on palpation of the right adnexal region. We advised conservative treatment with careful observation of the patient, in view of the possibility of an incomplete abortion or ectopic pregnancy. A Friedman test was negative. The patient improved after the reports were made to her local physician.

Five months later she returned with an identical story and slight bleeding of sixteen days' duration. A Friedman test was again negative. Dilatation and curettage and examination under anesthesia revealed no pathologic lesion.

A psychiatric consultation was obtained, and the patient rejected the psychiatrist and his advice. Special laboratory studies included a roentgen examination of the urinary tract, basal metabolism determination, and glucose tolerance test. The patient did not improve, and frequently demanded narcotics for the relief of pain. After three months she was again admitted to the hospital and an exploratory laparotomy was performed at the insistence of her family, her local physician, and the psychiatrist. The psychiatrist stated that the patient would never accept a diagnosis of functional disease until it was proved in this manner. No organic lesion was demonstrated at the time of laparotomy. An appendectomy was performed, and the superior hypogastric nerve was resected.

During her postoperative convalescence, the patient demanded large quantities of narcotics and rejected all attempts at psychiatric therapy.

She continued to complain bitterly of abdominal pain after she returned to her home and demanded narcotic drugs. Ten months after the initial consultation, she ingested a large quantity of analgesic and hypnotic drugs which she had accumulated in her home. Her family then committed her to a mental hospital for treatment. She has now remained well for two years following electric shock treatment and psychotherapy.

Surgical Management

The significance of functional pelvic symptoms in relation to major surgical treatment is indicated by the number of operations which had been performed on these patients without relief of the symptoms (Table XI). In fifty-one additional cases a major abdominal operation had been recommended before the patients were referred for consultation. In some of the patients this recommendation contributed seriously to the functional complaints which were present. In Group 2, ten of the 397 patients had sufficient pathologic abnormality to warrant a major operative procedure or were unable to accept conservative treatment. The operations performed were as follows: anterior and posterior repair 3, hysterectomy 5, removal of dermoid cyst 1, and myomectomy 1. On the recommendation of the psychiatrist a laparotomy was performed on three patients in Group 3 as part of their treatment. One typical case is reported. This recommendation is no longer accepted by our department. In numerous instances, however, a biopsy specimen was taken from the cervix. When necessary, this procedure was followed by cauterization of the cervix done in the office.

There can be little doubt that functional pelvic disease is responsible for many operations and may in part explain the poor correlation between the pathologic conditions reported and the operative procedure performed in the series reported by Miller¹⁰ and by Mengert.¹¹

TABLE XI. MAJOR SURGERY PRIOR TO CONSULTATION

	GROUP	2	3	TOTAL
Operation performed elsewhere without relief		92	49	141
Operation recommended elsewhere		44	7	51

Comment

There is no more distressing problem in obstetric and gynecologic practice than that of the patient who complains bitterly of persistent pain when no organic disease can be demonstrated. Of equal importance is a large group of patients with symptoms of far greater severity than can be accounted for by the organic changes which are observed. It is our purpose to relieve patients of their complaints. Frequently, operative treatment is required. Excellent results are obtained if the lesion corrected by operation was the whole cause for the patient's illness. On the other hand, an unnecessary operation may be performed for moderate pelvic disease if the emotional factor in the patient's symptoms is not appreciated.

Summary and Conclusions

1. A total of 2,315 white obstetric and gynecologic patients seen in a private diagnostic clinic was studied in regard to functional pelvic disease.

2. Three major groups were recognized: Group 1 (73.7 per cent) had organic disease sufficient to explain their complaints; Group 2 (17.2 per cent) had symptoms in excess of the demonstrable pathologic lesion; Group 3 (9.1 per cent) had pelvic symptoms without any abnormal findings.

3. Thirty per cent of the patients in Group 2 required special diagnostic studies to eliminate organic disease as a cause of their complaints. Most of the patients in this group had minor emotional problems which could be solved by simple psychotherapy. Out of the 195 patients in this group who were followed by us, 85 per cent obtained complete relief of symptoms, in spite of the persistence of organic disease in 108 patients.

4. In 209 patients (Group 3) no pelvic disease could be demonstrated, although multiple complaints were attributed to the pelvic organs. Special diagnostic studies were necessary to prove the absence of organic disease to 73 patients in this group. Of 86 patients in Group 3 whom we have followed, 53 per cent were relieved of their symptoms after simple office treatment. Fifty-nine of the patients in Group 3 were treated by a psychiatrist.

5. Only thirteen operations were used in the treatment of the patients in Group 2 or 3. One hundred ninety-two operations had been recommended or performed on these patients elsewhere.

6. We feel that the diagnosis of functional pelvic disease depends upon the absence of an organic lesion sufficient to explain the patient's complaints, and the presence of a distinct emotional problem. Our diagnostic approach is described.

7. The majority of patients with functional pelvic disease recognized their own emotional problem after proper explanation. The remainder required professional psychiatric care.

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Discussion

DR. WILLARD COOKE, Galveston, Texas.—For many years there has been an increasing recognition of the fact that the female reproductive tract is not an island isolated from the general physiology and pathology of the patient; in other words, that disease elsewhere may be reflected in genital symptomatology, and vice versa. In general, we are employing this knowledge in a fairly satisfactory manner, making it unnecessary to dwell further upon this point. It is only during the past few years, however, that the influence of the psyche has been increasingly understood and accepted. Unfortunately a great many of us still fail to evaluate and to correct the psychological element, and our patients are not relieved of what may be the major factor in their total subjective pathologic condition. We may perform a miracle of diagnosis and of operative cure in a case of some physical

pathologic state and yet leave the patient a hopeless, lifelong invalid because we have failed to employ appropriate prophylactic and curative psychotherapy of a very simple type. All of our splendid accomplishments are often undone by woman's worst enemy—other women—and if we fail to warn her of what she will inevitably be told and to convince her in advance that what she will be told is senseless and untrue. Similarly, the patient's own fears and misconceptions must be corrected before, during, and after her physical treatment.

We must constantly bear in mind that there are three types of pathology: the physical, the physiological, and the psychological, all three of which may coexist and any one of which may be the predominant factor in the patient's illness. If I may make a slight, but essential, correction of Dr. Lock's quotation, "Ninety-five per cent of the severity of human suffering is of psychological origin." For practical and definitive purposes, I have adopted the following classification of gynecic disease-states:

1. Purely physical pathology, e.g., frank acute salpingitis.
2. Physical pathology which is a by-effect of physical pathology elsewhere, e.g., the lutein-cystomatosis due to hydatidiform mole.
3. Physical pathology which is the by-effect of essential physiologic pathology, e.g., the hyperplasia of the endometrium which results from hyperestrinism, relative or absolute.
4. Purely physiologic pathology, e.g., simple menstrual aycelism.
5. Physiologic pathology which is a by-effect of essential physical pathology elsewhere, e.g., menorrhagia and other menstrual disturbances resulting from follicular cysts of the ovary.
6. Physiologic pathology which is the by-effect of essential physiologic pathology elsewhere, e.g., the genital dysfunction resulting from pituitary-hypothalamic dysfunction.
7. Physiologic pathology which is a by-effect of essential psychological pathology, e.g., the amenorrhea of exaggerated pregnophobia or desire for pregnancy, or of emotional shock.
8. Purely psychological pathology, e.g., pregnophobia, carcinomatophobia, frigidity, etc.
9. Psychological pathology due to the patient's knowledge of physical pathology, e.g., psychoneurosis based upon the knowledge of the existence of a tiny, symptomless, subserous fibromyoma.
10. Psychological pathology based upon physiologic pathology, e.g., premenstrual tension.
11. Mixed types, e.g., the climacteric syndrome with its physical atrophy, its physiologic dysfunctions, and its psychoneuroses.

Inextricably combined with all of these types is the mental illness of the patient which, in varying degree, may be minimal, considerable, dominant, or total.

As Dr. Lock has noted, the obstetrician-gynecologist is in by far the best position among the specialists for the correction of the wrong-thinking of the patient in most cases. He already has, unless he is a pure mechanist, the advantage of the full confidence of the patient and that peculiar emotional relationship which is so highly developed in gynecic patients. It is only when the psychological abnormality transcends the scope of knowledge and curative ability appropriate to our specialty that reference to the psychiatrist becomes necessary or even advisable—a fact which is being progressively realized and taught by the better minds among the psychiatrists themselves.

As Dr. Lock has also pointed out, the psychological factors must be detected, evaluated, and corrected if we are to fulfill our obligations under the basic principle of medicine: that the best interest of the patient supersedes all other considerations—in this instance of time, trouble, boredom, and lack of financial reward for the additional effort.

DR. RICHARD TE LINDE, Baltimore, Md.—Dr. Lock has talked about a phase of our speciality which has been greatly neglected. It is particularly neglected by the young

men and particularly by residents. They want to have as much surgical experience as they can out of their bed capacity and if a patient does not have gross pathology, out of the hospital she goes and is forgotten. I have always felt that no matter how busy or important a gynecologist may think he is, he should take his own history. He should get to know the patient psychically as well as physically in order to evaluate her. I have often found that after examining a patient and bringing her back into the examining room, she will tell her true story. Very often while you are looking her over she will be looking you over to decide if you are the right man in whom to confide.

I agree with Dr. Lock that major psychiatry should be done by psychiatrists, but I believe that much minor psychiatry should be done by the gynecologist and can be done by the gynecologist with less psychic trauma than some psychiatrists do to their patients.

There is always one thing which gives me concern when I think I have ruled out organic disease and that is the thought that I might be wrong. After all, no matter how clever one may think he is, we can all miss things on pelvic examination, and for that reason I recommend to you the use of the culdoscope. If you can look at the pelvic organs and be assured that they are just as normal as they feel to you, you strengthen your position with your patient. The reassurance you can give the woman because you have looked at the ovaries and tubes and uterus sometimes is all that is required to relieve her. At other times, the finding of a minor lesion may put you in a position in which you can tell the patient exactly what she has. We have used culdoscopy 186 times. The house men have used it mostly in suspected cases of ectopic pregnancies. In my own practice I use it chiefly in women with pelvic pain which I did not feel I could explain on pelvic examination, and it has kept me from opening many an abdomen. We have had no serious complications from its use.

PROF. JAMES YOUNG, London, England.—I suppose the subject we have had presented today may be thrown into the category of a condition which many of us have been conscious of for many years. I am at the moment thinking of the syndrome which Dr. Howard Taylor described in an interesting series of articles in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, in which he used the term "congestion fibrosis syndrome." It is interesting to recall that this condition in which you may get major symptoms in the absence of any pathologic abnormality or in the presence of only minor pathology has, as I have indicated, appeared in the literature—mainly the French and German—under varying designations, such as "chronic pelvic congestion," "chronic parametritis," and "congestive fibrosis syndrome."

I take it that we are today discussing a problem which has been present with us throughout the years and which has been in a sense one of the most despairing features of our clinical work. Indeed many of these women have passed through our clinics, receiving as much treatment as we could give them—very often operations which were futile—and have gone on into the subsequent period of their lives unrelieved and very often faced with a very unpleasing period of chronic poor health. I take it, as one of the speakers has indicated, that this is one of the most important problems we have to hand on to the younger gynecologists who are to succeed us. Whether or not in the majority of instances these symptoms can be attributed to psychosomatic factors is a matter which is not sufficiently proved. There is little doubt, however, that there must be a considerable residue which can be approached satisfactorily only by some such method.

DR. KARL WILSON, Rochester, N. Y.—This paper brings out what I emphasize to my students—and that is to see the patient as a whole. She comes into the gynecologic clinic with complaints referable to the pelvis, but there are other problems just as important, and I would like to describe an arrangement I have developed. We happen to have a very excellent psychiatrist and our relations are most cordial. I have sent two of my young men over to his department as a part of their training. That is of great value and it means

that our patients receive much more psychiatric attention than they did formerly. I am sure it has helped us solve many of our problems and it has kept many women from having unnecessary operations. I commend such an arrangement as being of real value.

SIR EARDLEY HOLLAND, London, England.—I would like to express my appreciation of the way in which Dr. Lock presented this important subject. The gynecologist must be a good all-round doctor to begin with, and with a little practice and a little elementary instruction he should be quite able to handle the psychological side of his patients himself instead of calling on the services of a psychiatrist. Many of our consulting-room patients suffer from emotional reactions and fear. A thorough, quietly taken history is an essential part of every gynecologic consultation. If that is done and the psychological conditions kept in mind, many common conditions, such as menstrual hemorrhage and irregularity and dyspareunia—especially in young women—will be found to have an emotional origin and can be cleared up with the utmost simplicity.

I would like to tell of one interesting case. I was asked by a well-known general practitioner to see a young married woman whose husband was Governor of a great Indian Province and she was, of course, the great social lady. She had to appear at many functions—garden parties, receptions, military reviews—at which she was the cynosure of all eyes and had to parade before everyone. I was told by the doctor that she had a retroversion of the uterus, severe backache, great lassitude, and such exhaustion that she often could not attend public functions, and that her husband was thinking of throwing up his career and returning to England. I asked the doctor if I could call again and see the patient by myself because that often ensures one getting a more complete history. Now, I had noticed her peculiarly thick and cylindrical ankles. You know that distressing condition some women have which is rudely called "beef to the heel," a thick pad of edematous fat extending from the level of the malleoli upward. I said, "What terribly thick ankles you have"; she burst into tears, and I knew then what her trouble was. This poor lady was so ashamed of her ankles that she dreaded to appear at important functions and had these protective break-downs. She had a retroversion too. I told the doctor that his patient had a retroversion but that had nothing to do with her symptoms, that her trouble was her ankles. Now, we had in Britain then a very skillful plastic surgeon, Sir Harold Gillies, and I told him the problem and he said he could fix it. He resected the layers of ankle fat and she left the nursing home with a pair of nice slim ankles. She went back to India and at once became a great social success. That is the kind of case Dr. Lock would appreciate.

DR. HANS KOTTMEIER, Stockholm, Sweden.—I have for many years been particularly interested in the subject just discussed. Our patients of juvenile age suffering from recurrent severe uterine bleeding have for a long time been treated with curettage, hormone therapy, blood transfusions, and so forth for functional bleeding without any effect worth mentioning before being referred to the Radiumhemmet for sterilization therapy with x-ray or radium. Now when these patients with recurrent bleeding come to the Radiumhemmet, they are subjected to a thorough examination. We feel there is often in patients suffering from severe uterine bleeding some link between the psyche and the uterine bleeding. We have treated the patient in consultation with the psychiatrist. Our treatment has been confined to taking care of the patient, attempting to remove as far as possible all outward irritations, and to do this we have worked closely with the parents, husbands, employers, and others who come in contact with the patient. The results have been remarkably good. In none of the patients has bleeding ceased entirely but normal menstruation has returned.

DR. LEWIS C. SCHEFFEY, Philadelphia, Pa.—We believe that in many of these patients there is a psychological difficulty based on sexual maladjustment and I wonder if Dr. Lock would speak more specifically on that problem.

DR. HOUSTON EVERETT, Baltimore, Md.—Dr. Lock has emphasized a very important group of patients, but I do not think the discussion should be closed without bringing up the possibility of urologic abnormality causing the symptoms. I think more such abnormalities will be found if the patients are investigated more thoroughly. It is recognized by many urologists, gynecologists, and obstetricians that chronic urethritis or interstitial cystitis or trigonitis can give rise to painful symptoms which cannot be differentiated in type from those arising in the genital tract.

DR. C. BECLERE, Paris, France.—In this difficult question of the diagnosis of functional troubles, we believe in Paris that the exploration with uterography is of great value. In some cases where physical examination shows us no gross pathologic abnormality, such exploration shows an unknown intrauterine lesion or an unknown intratubal lesion and in some cases an unknown tubosalpingitis. We treat these lesions, of course. On the other hand, in many cases with clinical troubles, radiological examination shows that the uterine cavity is normal and the tubes are normal. It is very important to show to the patient that she has nothing important that needs to be treated and especially nothing to be operated upon. We tell her that she can be treated medically and cured. In cases where the patient has been advised to be operated upon and we find nothing and in cases where the patient fears carcinoma and we find nothing on examination, it is important to be able to show her that the uterus is normal and the tubes are normal. When we can do this the patient is much relieved of her fear and very often the symptoms disappear. For all these reasons and from our experience of twenty-five years, we believe that uterosalpingography is a very good and practical diagnostic method.

DR. LOCK (Closing).—I cannot attempt to answer Dr. Scheffey's question relative to the frequency of sexual maladjustment in this group of patients in the available time. It is a common problem and we have been gratified that a large number of the patients completely recover when a specific emotional problem is found which can be corrected. Sometimes an apparently unrelated minor problem in the home will cause sexual maladjustment.

We are quite conscious of the frequency of gynecologic complaints resulting from urologic disease. Most of the patients in this category are included in Group 1. More urologic consultations are obtained than any other type on our service.

Dr. Te Linde and Dr. Wilson have both emphasized the importance of psychiatry in the gynecologic resident training program. It is our experience that private patients with functional pelvic complaints cooperate fully in most instances, and are anxious to be helped. However, those who come to charity outpatient clinics are likely to deliberately devise numerous complaints to avoid facing the responsibilities and duties of life in an underprivileged home. Therefore, a resident has much less chance to help his patient and is likely to lose interest in the problems of functional disease.

A NEW METHOD OF QUANTITATIVE ESTIMATION OF CEPHALOPELVIC DISPROPORTION*

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THE presence or absence of disproportion depends upon the relation between the size of the fetal head and the amount of space available in the pelvis, as determined in the individual case. It must be possible to measure both of these quantities accurately in any successful method of estimating degrees of disproportion, and the method described in this study allows this to be done. There are, however, at least two additional factors which influence the clinical significance of the measured degree of disproportion. These factors are (1) the quality of the labor, and (2) the ability of the fetal head to mold. Since these factors cannot be measured, it is impossible to establish hard and fast criteria of disproportion, because exceptions will sooner or later occur. This does not mean that the estimation of disproportion is without value. On the contrary, it means that recognition of the degree of disproportion will allow the purely clinical factors to be given their proper consideration.

The method of estimating disproportion described in this report supplies the obstetrician with two related items of information: (1) an accurate measure of the degree of disproportion in the specific case under consideration; (2) a statement of the statistical likelihood of safe delivery from below in the presence of a specific degree of disproportion. The decision as to method of delivery can then be made by considering these data together with all of the clinical findings.

Roentgenological Technique

The films consist of (1) anteroposterior stereoröntgenograms obtained by the use of a lumbosacral pad and slight elevation of the shoulders to give an adequate inlet view; (2) a standing lateral film with a plastic centimeter marker supported in the genital fold (Fig. 1); and (3) a view of the subpubic arch. The stereoröntgenograms are viewed in the precision stereoscope which by adjustment reconstructs an accurate three dimensional image of the fetal head and pelvis for visual "impressionistic" study and measurement. The precision stereoscope† has been used at the Sloane Hospital for Women for approximately fifteen years.

The films are taken at the time the question of disproportion must be decided, usually early in labor. Films obtained during labor have the added advantage that the fetal head does not move between exposures. After drying, the stereoscopic films are placed in the precision stereoscope‡ (Fig. 2). A study of the characteristics of the pelvis is first made and the observations are recorded.

*Read before the Seventy-Third Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. V., May 11 to 13, 1950.

†A new model of the instrument has been designed by the F-R. Machine Works, 4414 Astoria Boulevard, Long Island City, which calls for a change in the target-film and target-shift distances and in the technique for fixation of the stereoröntgenograms in the viewing cabinets. These changes will be described in detail by the manufacturer at a later date.

‡Wet films can be read quite satisfactorily but in borderline disproportion cases the dry films are preferred for accuracy in measurement.

These include classification as to type and the probable mechanism of labor. The degree of flexion of the head and its relation to the inlet are noted. The anteroposterior, widest transverse diameter, and interspinous diameter are measured directly from the visual image in the stereoscope.

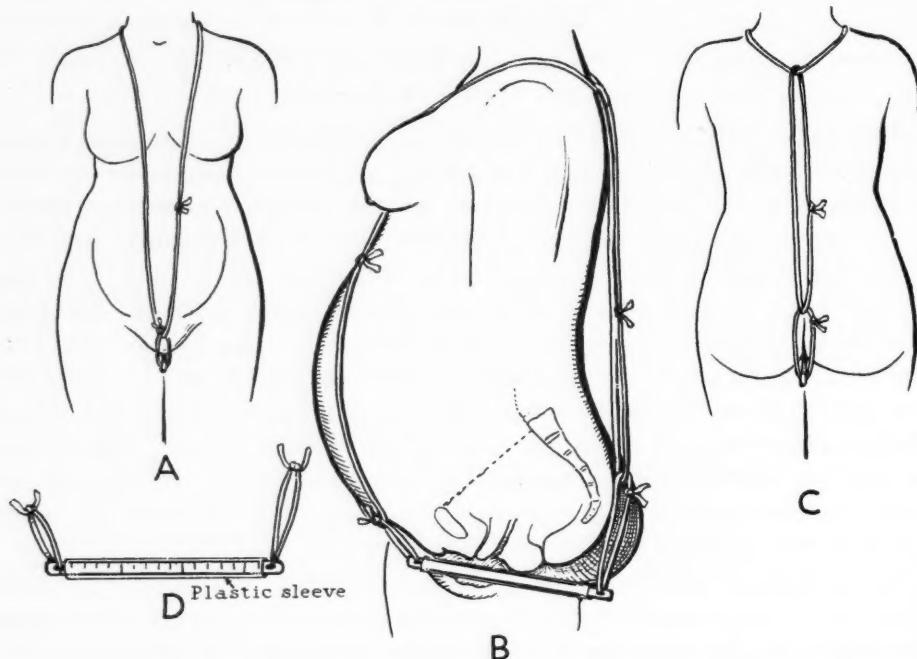


Fig. 1.—The genital fold centimeter marker D.* The anterior end is placed by patient in the genital cleft B. A long tape threaded through the posterior end of the marker follows the gluteal fold. A short tape through the anterior end extends above the symphysis. The marker is supported by long tape around shoulders as illustrated, A, C.

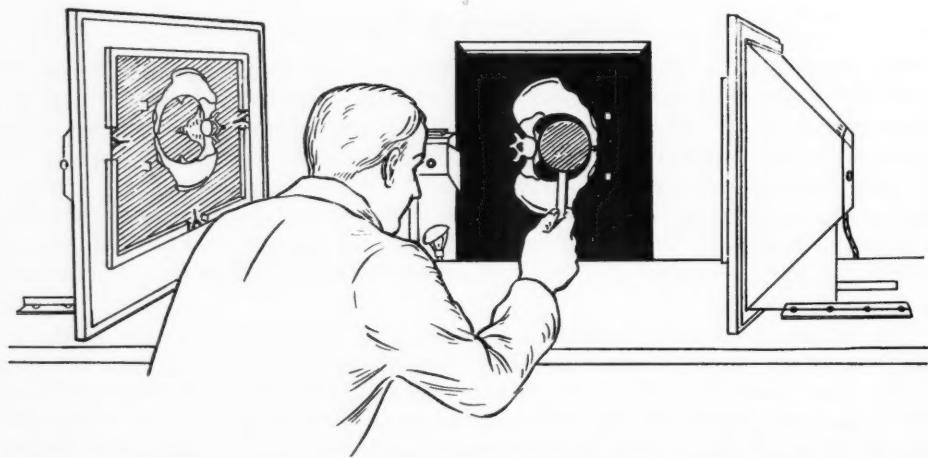


Fig. 2.—The precision stereoscope. The observer is using a circular disk to determine inlet size.

The lateral view is then examined with special attention to the level of the head and the characteristics of the sacrum. The anteroposterior diameter of the inlet is then measured by means of the gluteal fold marker. Experienced

*Supplied by F. R. Machine Works, 3930 Crescent St., Long Island City.

technicians have pointed out that it is difficult to position the patient, support a gluteal fold marker and at the same time obtain consistently satisfactory lateral roentgenograms. Slight rotation of the patient introduces inaccuracy in measurement of the anteroposterior diameter of the inlet by means of the gluteal fold marker. The marker as illustrated in Fig. 1 satisfactorily overcomes these disadvantages. The anterior portion of the gluteal fold marker is placed in the genital cleft by the patient. A long loop of tape fixed to the posterior end of the marker follows the gluteal fold and aids in maintaining the sagittal plane. The anteroposterior diameter of the inlet obtained in this way serves as a check upon the accuracy of the measurements obtained by the precision stereoscope. For instance, in certain instances the region of the promontory is not clearly shown in the stereoscopic films or slight movement of the patient between exposures may give a pseudostereoscopic effect. For these reasons this correlation of measurements by two pelvimetry techniques is an important part of the examination.

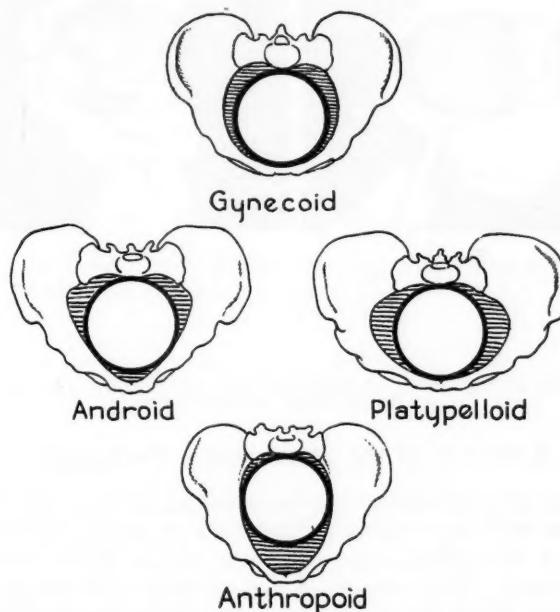


Fig. 3.—The circle index of inlet size for the parent pelvic types. The compensatory space is shown for each type and is more significant in gynecoid and flat forms. This compensatory space as illustrated cannot be measured except by "impressionistic" methods (visual study of inlet shape).

Method of Estimating Disproportion

For the purpose of estimating degrees of disproportion there have been constructed a set of cardboard circles of known diameters, graduated from 8.0 cm. to 12.5 cm. in 0.25 cm. intervals. These are mounted on wooden handles for easy use. With the image well visualized in three dimensions in the precision stereoscope, a circle is carried into the image and placed in the plane of the inlet. Various circles are tried until one just fits the inlet as shown in the diagrams, Figs. 2, 3, and 4. When of the proper size, the circle should touch the pelvic inlet at two or three places, usually at the junction of the first and second sacral segments posteriorly, and the two sides of the forepelvis anteriorly. It must not overlap at any point. The manner in which the circle fits the four main types of pelvic inlet is shown in Fig. 3. It may be necessary to interpolate

for inlets which none of the cardboard circles fits precisely, but this is not difficult. The diameter of the circle is then noted.

A cardboard circle is next carried into the image of the head and placed perpendicular to the longitudinal axis of the head. The circle is moved along this axis until it lies in the plane of the biparietal or suboccipitobregmatic diameter. The circle is varied until one is found which fits the image at this plane (Fig. 4, B). Interpolation may again be necessary. The diameter of this circle is then noted.*

The diameter of the circle for the head is then subtracted from the diameter of the circle for the inlet. This gives a *difference* which is the significant figure of the method.

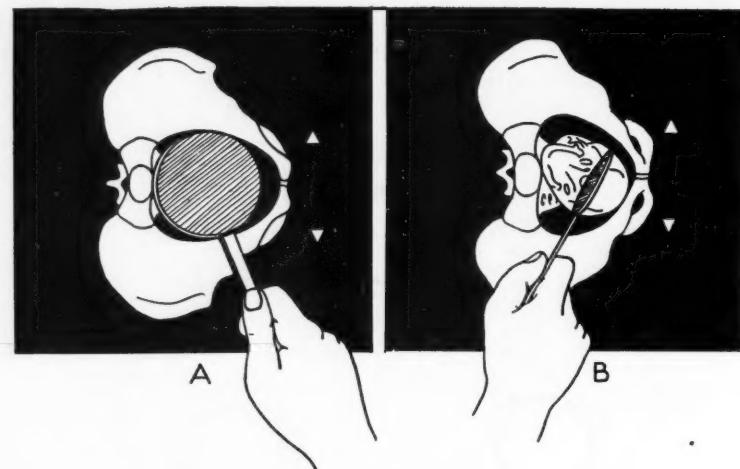


Fig. 4.—A, Circular disk giving index of inlet size for anthropoid type of pelvis. B, Circular disk giving index of head size.

Accuracy of the Stereoscopic Technique

The accuracy of this technique has been tested in three ways. First, skeletal pelvises were x-rayed and the various diameters as measured in the stereoscope were compared with the actual measurements of the bony pelvis. A variation of ± 1.0 mm. was found. Next, repeated measurements of actual clinical material were made. In these films the maternal soft tissues produce some decrease in the clearness of the final image, but the variation of repeated measurements was again found to be ± 1.0 mm. Finally, the fetal head was measured in the films and the measurement compared with the actual diameter of the head in those cases where delivery was by elective cesarean section. After correction for the thickness of the scalp (2.0 mm.) this figure is subject to a variation of ± 2.0 mm.

From these determinations it is justifiable to assume an error of ± 1.0 mm. for the pelvic measurements, including the circle of the inlet, and an error of ± 2.0 mm. for the circle of the head. There results an experimental error of ± 3.0 mm. for the *difference*.

Material

The patients studied by this method were all delivered at the Sloane Hospital for Women between the years 1937 and 1949. It is not the policy of this

*The biparietal or suboccipitobregmatic may be readily seen in some instances, but in other cases neither of these diameters is apparent. The shadow cast by the head does not allow three-dimensional visualization as sharp as that of the pelvis, so that the diameter measured by the circle cannot always be specifically recognized. In this event, however, it is always possible to measure at the level of the plane of the biparietal. The resulting measurement will either be *equal* to the biparietal or *larger* by 1 or 2 mm.

hospital to take routine x-rays, so that the patients on whom x-ray pelvimetry is performed represent a selected group in whom some degree of disproportion is suspected. In order to determine whether criteria of disproportion could be established, it was necessary to carry the selective process further. Cases of elective cesarean section, and of cesarean section for causes other than bony disproportion, were excluded.* Cases with poor films, and with x-rays obtained more than two weeks before the time of delivery, were also excluded. This left two chief groups of cases: those patients who had been delivered from below under the stress of labor, and those who had been unable, during an adequate trial of labor, to engage the head and allow either spontaneous or forceps delivery. The total number of cases reported is 911, of which 94 required cesarean section, while in 817 delivery was from below.

A most difficult decision in this study was to determine what constitutes an adequate trial of labor. No fixed standard has been established at the Sloane Hospital for Women. The trial of labor is terminated when it has been determined, by repeated examinations, that *no progress is being made*. One patient in this group was fully dilated within four hours, others never achieved full dilation. The lengths of the trials of labor varied from 5 to 56 hours, the mean being 16 hours and the median 12 hours, but in every case the attending obstetrician was satisfied that clinically good labor had been present for a sufficient period of time to produce engagement if engagement were going to occur.

Inlet Disproportion

The relation between the degree of disproportion as calculated in this manner and the outcome of labor is shown in Table I.

TABLE I. METHOD OF DELIVERY WITH VARIOUS DEGREES OF DISPROPORTION AT THE INLET

DIFFERENCE AT INLET	METHOD OF DELIVERY				PROBABILITY OF CESAREAN SECTION
	TOTAL CASES	MID FORCEPS*	CESAREAN SECTION AFTER TRIAL OF LABOR	SPONTANE- OUS OR LOW FORCEPS	
1.0 cm. or less	58	5	48	5	5:1
1.1 cm.-1.4 cm.	43	4	29	10	2:1
1.5 cm.-1.7 cm.	58	13	11	34	1:4
1.8 cm. or greater	752	30	6†	716	0
Total cases	911	52	94	765	

*Includes 1 case of high forceps.

†Includes 5 cases of uterine inertia without disproportion and 1 case of midpelvic disproportion.

The difference here measures disproportion at the inlet, and the significance of this correlation is best seen in the column headed "Probability of Cesarean Section." Four arbitrary groups have been chosen. In that group with the difference 1.0 cm. or less, the probability of cesarean section is 5:1. This is the "absolute disproportion" group. A further description of this group is necessary in order to support the use of this term. There were 10 deliveries from below in 58 cases. Of these deliveries, there were 4 midforceps, 1 high forceps, and 5 spontaneous deliveries. These resulted in 4 stillbirths (1 high forceps, 2 midforceps, 1 spontaneous), all with intracranial injury. Another child, delivered by midforceps, was greatly shocked and was in a critical condition for one week, but went home apparently well. Thus, there were 5 normal

*This excludes 89 per cent of the cesarean sections.

children born from below in 58 cases in this group, and this seems to us to be too small a chance of success to warrant attempts at vaginal delivery.

On the other hand, the 6 patients who were successfully delivered from below are of some interest. There were 5 young Negro primiparas in this group, and one Puerto Rican multipara. All had flat or flat gynecoid pelvis. All had extremely powerful labor. Since these patients were delivered from below, it appears that this combination of clinical factors might indicate a trial of labor in these particular circumstances, with an increased chance of success. The Negro infant's head molds more easily and more safely than does that of the white infant, so that another factor tending toward delivery from below is added. But there were at least 5 patients also studied who met all of these criteria and yet required cesarean section, so that even under the most "favorable" circumstances the chance of safe delivery from below, with a difference of 1.0 cm. or less, is not great.

At the other end of the scale are 752 patients with a difference of 1.8 cm. or greater. There were 6 cesarean sections in this group, 5 for pure uterine inertia and one for midpelvic disproportion. All of the remaining 746 patients were delivered safely from below, with no clinical signs of disproportion at the inlet. This indicates that *no* disproportion exists when the difference is 1.8 cm. or greater.

Between the absolute disproportion group and the no disproportion group lies the borderline group, with the circle difference between 1.1 cm. and 1.7 cm., inclusive. There are 101 cases in this group, of which 40 required cesarean section. The probability of cesarean section is better seen, however, by dividing this group into two sub-groups, one of "high borderline" and the other of "low borderline" disproportion. In the high borderline group there are 43 cases, of which 29 required cesarean section. This represents a probability of cesarean section of 2:1. In the low borderline group there are 58 cases, of which 11 required cesarean section, for a cesarean section probability of 1:4.

Midpelvic Disproportion

It is extremely difficult to make a quantitative estimation of the degree of disproportion in the midpelvis, because of the peculiar shape of the area. It is quite possible to measure the interspinous diameter, and to measure certain anteroposterior diameters located in the sagittal plane. It is *not* possible to fit a circle to the midpelvis, as may be done at the inlet. Furthermore, it may be demonstrated on skeletal pelvises that when arrest occurs in the midpelvis the head is obstructed anteriorly by the descending rami of the pubes, at a point some two-thirds of the distance from the symphysis to the tuberosities. This anterior line of obstruction lies in a plane passing through the spines and parallel to the plane of the inlet. The head actually projects beyond this line into the subpubic arch, so that the anterior limit of this plane is a curved area in space. The amount of space available anteriorly thus depends not only on the distance from the interspinous diameter to the posterior aspect of the pubic rami but also on the width of the subpubic arch. Unfortunately, no means of measuring the anteroposterior limits of this plane have been devised.

Since the circle concept cannot be applied to the midpelvis, an estimate of the degree of disproportion can be obtained by subtracting the diameter of the fetal head (as determined by the circle) from the values of the individual diameters. When this is done for the interspinous diameter the results shown in Table II are obtained.

While this group of cases is relatively small, it is seen that the probability of midpelvic arrest increases as the difference at the spines decreases in value.

But this difference measures only the degree of disproportion in the transverse diameter, and the anteroposterior diameter is equally important. When the diameter of the head is subtracted from the various anteroposterior diameters, however, no general correlation can be obtained which would allow the establishment of numerical criteria of disproportion. It is necessary, therefore, to resort to a description of the characteristics of the sacrum and the subpubic arch in order to estimate the possibility of arrest. The inclination of the sacrum can be described as forward, average, or backward. Its curvature can be described as straight, average, or marked. The subpubic arch can be described (by clinical examination best of all) as narrow, average, or wide. When the difference at the spines is less than 1.8 cm., the widest diameter of the head cannot pass through this diameter, and the head must therefore pass either before or behind this diameter. If the sacrum is straight and inclined forward, and the subpubic arch is narrow, a dangerously high degree of disproportion will exist at this level. If, as is seen in many anthropoid pelvis, the sacrum is inclined far backward and has a marked curvature, the head can pass posterior to the spines and spontaneous delivery will occur despite a numerically small value for the difference at the spines.

TABLE II. METHOD OF DELIVERY WITH VARIOUS DEGREES OF DISPROPORTION AT THE INTERSPINOUS DIAMETER

DIFFERENCE AT SPINES	METHOD OF DELIVERY			PROBABILITY OF MID FORCEPS
	TOTAL CASES	MID FORCEPS	SPONTANEOUS OR LOW FORCEPS	
1.0 cm. or less	14	13	1	13:1
1.1 cm.-1.4 cm.	14	9	5	2:1
1.5 cm.-1.7 cm.	12	7	5	3:2
1.8 cm. or greater	36	2	34	1:20
Total cases	76	31	45	

The forward lower sacrum seldom produces obstruction by itself unless the tip closely approaches the spines. The degree to which the sacrum comes forward can be measured in the standing lateral film by drawing a line through the tips of the spines perpendicular to the plane of the inlet. When the distance from the tip of the sacrum to this line is less than 2 cm., arrest has invariably occurred. Whether this arrest can be easily and safely overcome depends upon the difference at the spines and the width of the subpubic arch.

It is rare to perform a cesarean section for a narrow interspinous diameter or a markedly forward lower sacrum when these deviations from the normal are associated with an adequate inlet. However, when the biparietal diameter of the head equals or exceeds the interspinous diameter, cesarean section may be the method of choice for delivery. It should be realized that extreme deviations from the normal in the mid or lower pelvis are commonly associated with restriction in inlet space and cesarean section is indicated for the inlet disproportion rather than for the lower abnormalities.

Comment

It is possible by the described technique to measure the degree of disproportion at the inlet and the midpelvis, and from this to calculate the probability of safe delivery from below. The decision as to method of delivery can then be made by considering this information together with all of the clinical findings

in the individual case. The results of x-ray pelvimetry must not be allowed to overrule the clinical findings, nor, on the other hand, should the purely clinical approach be allowed to overrule the x-ray findings.

The prognosis made by x-ray pelvimetry is dependent upon the forces of labor, and these forces will produce deviations from the expected outcome of labor. It is obvious that a forecast of spontaneous delivery is contingent upon the occurrence of normal labor. Powerful labor will overcome higher degrees of disproportion than will feeble labor, so that when borderline disproportion exists the final outcome may well be determined as much by the powers as by the passages. It is this variation in the efficiency of labor, which cannot be measured quantitatively, that produces certain of the exceptions to the x-ray prognosis. But very powerful labor, capable of overcoming high degrees of disproportion, is not always desirable. Powerful labor overcomes disproportion by producing extreme molding of the fetal head, and this molding can be so great as to result in intracranial damage and death of the fetus, even with a spontaneous delivery.

It seems wise, therefore, to give considerable weight to the x-ray findings when a very high degree of disproportion is present. These cases are best treated by cesarean section, for the chance of delivery from below is quite small, and the risk to the child with delivery from below is quite large. Delivery from below in such cases is certainly occasionally possible, but it may not seem worth the risk.

When borderline disproportion is present, the clinical factors, especially the quality of the labor, will carry most weight. In general, a trial of labor is indicated in most of these cases.

When no disproportion is present, the clinical factors are all important. Uterine inertia and other complications of labor will occasionally require cesarean section, but all efforts toward delivery from below can be carried out with the knowledge that the pelvis will offer no obstruction.

How this, or any other, method of estimating disproportion is used will depend on the philosophy of the individual obstetrician. Cesarean section has been made safe for mother and child, when performed under the proper conditions, and it seems an easy way out of obstetrical difficulties, especially disproportion. On the other hand, a small but very real risk from rupture of the uterus in subsequent pregnancies is produced. Traumatic delivery from below carries danger to the child and the mother, and reduces the probability of future childbearing. In balancing the various possibilities one against the other, it is of some value to be able to measure quantitatively one of the factors on which the final decision must be made.

Discussion

DR. HERBERT F. TRAUT, San Francisco, Calif.—Over the years we constantly strive to solve the problems of childbearing. Whereas, in recent years the emphasis has been greatly placed upon hemorrhage and infection, with very substantial rewards in reducing maternal morbidity and mortality, we have now to seek similar reductions in fetal mortality and fetal damage. Hence the work of which we have just heard the barest outline is most welcome and most necessary.

Following as it does, by several years, the notable contributions of Caldwell and Moloy, we are most privileged to hear of this extension of the work begun so long ago. The report represents more than 12 years of work in applying the principles involved to the solution of pelvic problems as presented by almost 1,000 patients. The size of the material presented is more than sufficient to make the authors' deductions valid from the point of view of statistical significance. That these workers could have labored silently for so long without giving some indication of their beliefs is a tribute to their desire to achieve sound conclusions. We must, in all admiration, give the authors credit for this outstanding evidence of reticence which of course adds materially to the conviction with which they speak to us.

The method they use for estimating disproportion would seem to be a practical one—very concrete and not too mathematical. We are most impressed with the results of its application when, as in Table I, it is translated into terms of the statistical probability of a difficult midforceps as offset by the possibility of a cesarean section. They wisely admit that there are intangible factors, such as the efficacy of labor and the dilatability of the cervix as well as the moldability of the presenting part. Thus they leave us, generously, a vestige of the ancient art of obstetrics. But actually, while making a distinct contribution, they leave us more in doubt than the title of the paper might suggest, in the matter of individual obstetrical judgment.

As they progress in their thinking, the emphasis placed on fetal mortality rather than maternal mortality certainly follows the modern trend. They consider a cesarean section to be as safe for the parturient mother as a difficult midforceps delivery, and at least 10 times safer for the infant. In this we heartily agree.

The data in Table II afford a correlation of values, as they relate the interspinous diameters to the fetal headsize. This is done in contrast to the old custom of placing emphasis upon an arbitrary figure for this measurement, as we have been prone to do in the past. The effort made is a laudable one, and in time will surely lead to reliable data which will be of help to all.

On the other hand, although we have had some experience with the precision stereoscope and its application to pelvic problems, we are inclined to feel that, except in the hands of experts, the elements considered as pertaining to midpelvic disproportion are a little more ambiguous than we had hoped they might be. They are not an exact measurement. However, with constant application the methods advocated may enable one to approach nearer the true estimation of the situation. The midpelvis, as Mengert and others have repeatedly insisted, can be just as deadly as the pelvic inlet and far more so than the pelvic outlet. The midpelvis is much more difficult to evaluate than either of these. The authors have offered us a method which tends toward more adequate evaluation of this zone, but it would seem that much practice must have been achieved to warrant the expectancy of the results they report.

The authors' conclusions regarding the dependence to be placed upon x-ray findings are sane. They follow our own conservative attitude for the most part. They, as we, would much rather make our own deductions from the roentgenogram than to depend upon a roentgenologist to do it for us.

Increasing emphasis upon long-term fetal salvage toward the production of useful members of society is the rule these days and very properly so.

In conclusion, it would seem reasonable to predict that, if one had a precision stereoscope at his disposal—a prime requisite which the authors take for granted, by the way—adherence to the reasonable recommendations of the authors would result in increased fetal salvage, without increasing maternal risk or harm.

DR. RALPH REIS, Chicago, Ill.—Dr. Moloy has made another valuable contribution to the study of the relative size of the pelvic inlet. I would like to comment on the term "cephalopelvic disproportion" which is used carelessly in too many places. For a number of years every patient taken to the operating room at Michael Reese Hospital for cesarean section with a preoperative diagnosis of cephalopelvic disproportion has the internal con-

jugate measured directly in the operating room and the biparietal diameter of each baby is likewise measured in the operating room. We find that, in something better than 90 per cent of these patients with a diagnosis of cephalopelvic disproportion, the biparietal diameter is the same size or smaller than the internal conjugate. We have come to the conclusion that, except in true contracted or malformed pelvis, failure of engagement of the fetal head is due to many other factors, such as fetal size, moldability, and, most important, inefficiency of uterine contractions.

DR. THADDEUS MONTGOMERY, Philadelphia, Pa.—I wish to join the other discussers of this paper in pointing out the important contribution that Dr. Moloy has made to the study of disproportion. The prognostication of how the fetal head will behave in the presence of certain anatomical peculiarities of the female pelvis has been of considerable value to the clinician.

Roentgenologic diagnosis, however, has not made it possible to determine what will happen in labor in the presence of moderate cephalopelvic disproportion. The solution of absolute disproportion is easy. The estimation of all those factors which enter into successful result in moderate disproportion is difficult. Consultation between the radiologist and the obstetrician is essential, and the repetition of films during the course of labor is important in determining progress as uterine contractions become effective and forceful.

The introduction of, and the wider acceptance of, extraperitoneal cesarean section have made it possible to observe a considerable number of these patients for a somewhat longer period during labor than we have been accustomed to in the past. Perhaps it has led to a renaissance of the so-called test of labor in which the clinician assumes from his preliminary studies that delivery may take place through the vaginal route, but may have to reverse himself at a later stage, and deliver the patient by abdominal section. Our results with extraperitoneal cesarean section in such situations have been most satisfactory. Unless we resorted to such procedure, the percentage of cesarean sections in moderate disproportion, particularly in the Negro population, would be very high.

While x-ray pelvimetry has been of considerable assistance in the diagnosis and prognosis of head-first labors, yet, thus far, not much help has been presented in the solution of the breech presentation in which the mechanical difficulties are considerable, and in which the effective comparison of head size and pelvis size is much more difficult. I should like to ask Dr. Moloy whether in his recent studies he has been able to make any further contribution to this still difficult problem of breech labor.

DR. L. A. CALKINS, Kansas City, Kan.—I do not by these few remarks wish in any way to minimize the importance of Dr. Moloy's observations.

I would like to substantiate further what has been said by Dr. Reis and Dr. Montgomery. The country over, too much emphasis has been placed on x-ray pelvimetry which to me becomes important in only a very small percentage of our obstetric cases. Too little emphasis has been placed upon the physiologic factors concerned in labor. At the moment, as Dr. Reis has pointed out, we are most concerned with the forces of labor and, as supplemented by the remarks of Dr. Montgomery, the alterations in position of the presenting part. Like Dr. Montgomery, I am very much concerned in these relatively small pelvis with breech presentation about which, it seems to me, we know least of all. I am, therefore, particularly happy that Dr. Moloy has finally brought into his consideration the forces of labor which may and do materially alter the outcome.

We used to believe the old adage that good pains will cure almost anything. That is not quite true, but it is certainly true that poor pains will make a situation completely impossible when otherwise it might be comparatively favorable.

I would like to agree with Dr. Montgomery that unless and until we know the kind of forces available in labor, we cannot come to a final decision. Moreover, pelvimetry done a month or two months before labor often means nothing, and I would like Dr. Moloy to comment on that point because I happen to know he is very much interested in pelvimetry done during the course of labor.

DR. EDWARD L. KING, New Orleans, La.—I merely want to emphasize what has been said regarding labor itself. One of my associates recently reviewed 1,000 of our private cases that had been studied by roentgen rays by the method of pelvimetry in use in our part of the country and he emphasized that sometimes these studies do not mean much as labor progresses. Another point he thinks is important is the moldability of the fetal head under the influence of satisfactory labor pains. He made an estimate—which may be wrong or right—that the fetal head can be safely molded without damage to the fetus, under the influence of labor pains, to the extent of 25 per cent. More than that would be dangerous. How we can estimate that is another story. We have various ways of estimating the size of the fetal head in comparison with the size of the pelvis, and if there is not more than 25 per cent discrepancy he felt it could make the grade. That may be wrong or right and time will tell.

I feel as Dr. Calkins does that throughout the country too much reliance is put on x-rays and pelvimetry alone. Frequently we find that the roentgenologist, who is not too well versed in our field, tells us that this baby can get through or cannot get through. He too often is the one who does not know his own business and certainly knows nothing of obstetrics.

I would like to have Dr. Moloy say something about the aftercoming fetal head in breech presentation in the narrow pelvis. If he can solve that problem he will relieve us of many headaches.

DR. JOSEPH L. BAER, Chicago, Ill.—I wish that someone would emphasize the fact that in the end the clinical evaluation of the possibility of vaginal delivery must take precedence over the roentgenologic findings. In those instances in which there is adequate roentgenologic facility available, the roentgenologic findings are thrust into the foreground and too often they mislead the clinician who feels insecure about his clinical problem.

I should also like to have the point emphasized that the basic value of roentgen studies clinically comes about during the progress of labor.

DR. SAMUEL COSGROVE, Jersey City, N. J.—I should be most happy to emphasize the two points Dr. Baer has suggested. We have been following the work of Dr. Caldwell and Dr. Moloy ever since they first began to publish it. Their work has been of tremendous help to us, yet, as Dr. Baer and the other discussants have indicated, the shadowgraph of the bony pelvis is not a reliable measurement of the capacity of an individual woman to deliver an individual baby. It is, in our experience, merely a means of putting a man on the *qui vive* if he is to be responsible for the management of labor. Any obstetrician who takes the say-so of a roentgenologist as to whether a particular baby can traverse a particular pelvis is a fool.

Dr. Calkins suggested that a roentgenogram taken several weeks before labor is not necessarily a measurement of what will happen at the time of labor. In other words, if you correlate those x-ray findings to the labor you will have to do it on an entirely hypothetical basis; that is, you will say that this pelvis will probably transmit a hypothetical baby of average size, calling the average size what you will, 6½ pounds or some variant from that figure. But what the baby will weigh and how it will approach that pelvis and with what force the uterus will act as it approaches the pelvis are the determining factors to be measured by observing that woman in labor.

Dr. Moloy has increased our knowledge of the configuration and mensuration of the pelvis by this study. I hope he will continue to strengthen those factors of his work which he acknowledges are weak. I am glad to have him acknowledge in his work the importance of the other factors of labor and to express his conclusions in terms of probability and not actual potentials.

DR. CALKINS.—I would like to ask Dr. Cosgrove about the effect of analgesics and anesthetics on labor pains in these particular patients whose pelvis are under question.

DR. COSGROVE.—That again is a matter of absolute individualization. No formula can be expressed for it. Generally analgesia must not be overdone. On the other hand, one frequently finds that with an analgesic, and particularly morphine, there will be great expedition of labor in certain situations.

DR. J. ERIC STACEY, London, England.—My small contribution to this discussion is to emphasize the fact that we are dealing with an art and not a science. We must remember that the baby's head in the passage through the channels is not bone to bone but the mother has soft parts which must be taken into consideration and evaluated. Dr. Moloy's contribution has been of great value in showing us the shape of the pelvis rather than the size of the pelvis, and it is the shape that matters more than the size in the passage of the baby's head. We do not know the position the baby's head will take in its passage through the pelvis and there is no predetermining factor to tell us.

Two things we must remember: Do not let the radiologist become the obstetrician, and do not let a trial of labor become a trial of fortitude.

DR. MOLOY (Closing).—A long labor, in most instances, indicates the presence of disproportion at the inlet or at lower levels. A long labor is essential to allow adequate molding of the fetal head. Forceps are hazardous to the infant. Cesarean section may become the method of choice, under these circumstances, when roentgen methods of examination give the existing degree of disproportion and statistical studies reveal the probabilities for safe delivery from below.

I believe that we should realize that disproportion at the present time is quite different from the extreme degrees encountered years ago when rickets and other causes of extensive deformities were more prevalent. We are interested more in obtaining a healthy mother and infant and this factor is considered in correlation studies in regard to disproportion and outcome of labor.

Dr. Reis has asked for a definition of disproportion. This question is difficult to answer because we have observed instances in which a child has been delivered by efficient labor with a biparietal diameter larger than the anteroposterior diameter of the inlet. As a rule, the head is usually smaller than the inlet size, as Dr. Reis has found by measurement at the time of cesarean section (1 cm. difference or less).

In regard to Dr. Calkin's comments, we approve the use of x-ray methods at term or in early labor. In our so-called x-ray room we discuss problems in the mechanics of labor. We believe that these discussions have educational value for the resident and intern and opinions expressed under these circumstances are not necessarily carried into and applied in the labor room.

The precision stereoscope is expensive and many people find it difficult to visualize stereoscopically, and the average resident requires several months of supervised instruction before he can measure the phantom image with accuracy. It has been difficult to interest a manufacturer in the instrument but we expect to receive an experimental model in the near future and the instrument itself will be available for purchase within six months.

Attempts at measurement of the fetal head in breech presentation have not been successful. We carefully appraise the pelvis and base prognosis upon the assumed size of the fetal head.

EXPERIMENTAL ENDOMETRIOSIS*

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(From the Department of Gynecology, the Johns Hopkins University School of Medicine and the Johns Hopkins Hospital)

THE diagnosis of endometriosis is clinically increasing as shown by Scott and Te Linde.¹ There is some doubt as to whether this increase is an actual one or is due to an increasing ability to recognize the disease process. As a condition in which tissue resembling uterine mucous membrane is found in ectopic locations, particularly the pelvis, it occupies a unique place in gynecology. It is a benign growth of an adult tissue which spreads and infiltrates into adjacent organs in a manner analogous to malignant tissue. It may be silent symptomatically or it may produce variable and often incapacitating clinical complaints. Sterility is a result of its pelvic devastation or the necessary corrective surgery is most distressing. It behooves the gynecologist to uncover more fundamental information in order that the disease may be prevented or more adequately treated.

Theories of Etiology of Endometriosis

Brooks Ranney² has recently collected and summarized the experimental and clinical data supporting each of the various theories. The extent of the data attests the interest in the disease and the conflicting conclusions support the lack of unanimity. Two major theories have been widely advocated, but most writers on the subject agree to the possibility that no one theory can explain all cases.

From 1921 until his death in 1946, Sampson³⁻⁹ studied and wrote extensively on this subject. He postulated the interesting theory of retrograde flow of menstrually discharged endometrial particles out of the fimbriated end of the tube, with consequent implantation and growth of these particles. He felt that secondary implanting could occur by "showering" from "incubated" primary pelvic growths. In favor of this theory were the following:

1. The similarity in histological structure and function between the implants and the uterine mucosa.
2. The observation of blood and endometrial particles coming from the fimbriated ends of tubes exposed by operation at the time of menstruation.
3. Patency of the tubes in 284 of 293 patients with endometriosis.
4. The distribution of pelvic endometriosis, which is what one would expect if retrograde menstruation were the cause.
5. Growth of endometrium in animal experiments when implanted into the peritoneal cavity.
6. The fact that pelvic malignancy spreads and implants in a manner somewhat similar to endometriosis.

*Read at the Seventy-Third Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 11 to 13, 1950.

Sampson suggested in later papers the possibility of additional explanations, such as metaplasia of the epithelium in amputated tubal stumps, metaplasia at the endosalpingeal-peritoneal junction, and venous and lymphatic spread. He firmly supported his primary theory of retrograde menstruation and in 1940 said: "If bits of Müllerian mucosa carried by menstrual blood escaping into the peritoneal cavity are always dead, the implantation theory, as presented by me, also is dead and should be buried and forgotten. If some of these bits are even occasionally alive, the implantation theory also is alive."



Fig. 1.—Sagittal drawing of endometriosis in an autopsied monkey three years following a hysterotomy to recover an early embryo. The large endometrial nodules are seen above the uterine fundus and endometriosis can be seen penetrating the bladder.

The second major theory of the cause of external endometriosis postulates abnormal differentiation of the celomic epithelium, the epithelium which is the embryological source of the genital mucous membranes. This is commonly called the celomic metaplasia or Iwanoff-Meyer theory, and it has received its greatest support from Novak. Proponents of the celomic metaplasia theory give the following as supporting points:

1. Menstruating endometrium is cast off and dead, therefore incapable of growing on the pelvic structures.
2. It is difficult to conceive of such endometrium as being capable of passing against the current, through the minute isthmic portion of the tube, and then viably implanting.
3. Retrograde menstruation is rarely observed.
4. This theory would give a tenable explanation for the more rare locations of endometriosis, such as in the umbilicus and extremities (see Gruenwald¹⁰).

In appraising these two theories, it can be readily seen that the first major question to be settled is the status of castoff endometrium—is it viable or is it dead? Meyer¹¹ has stated that if the viability of menstrually discharged endometrial particles could be definitely proved, the first question concerning the implantation or Sampson's theory would be answered.

The *Macacus rhesus* monkey was chosen as the experimental animal in these studies for several reasons. Since the female rhesus monkey is a cyclically menstruating animal, the genital physiology is closely akin to that of the human



Fig. 2.—Drawing of endometriosis involving intestines and lower abdomen of a monkey approximately three years following a hysterotomy to recover an early embryo.

female. Jacobson¹² has shown that endometrium is viable in the pelvic cavity of this animal when implanted. One of us (R. W. Te Linde) working with Hartman,¹³ found extensive endometriosis two to four years after hysterotomies were done on pregnant monkeys in order to recover early embryos. (Figs. 1 and 2.) Fraser¹⁴ reported a case of spontaneous endometriosis in a rhesus monkey autopsied at a London zoo. To our knowledge this is the only instance of spontaneous endometriosis in an animal below the level of the human female.

Experiments With Undesquamated Endometrium

There is no doubt from experimental studies that endometrium cut from the uterine lining and transplanted in the pelvic cavity or other areas will grow. Harbitz,¹⁵ Allen,¹⁶ Weinstein and collaborators,¹⁷ Hobbs and Bortnick,¹⁸ and numerous other workers have successfully transplanted surgically removed pieces of endometrium in lower animals. Jacobson¹² did extensive studies on trans-

planted endometrium in rabbits and monkeys. Markee¹⁹ did his careful studies on menstruating endometrium by using eye anterior chamber endometrial transplants in the monkey. Heim,²⁰ Caffier,²¹ Traut,²² Hirsch and Jones,²³ and others successfully cultured endometrium obtained from surgically removed uteri.

In order to confirm again the viability of transplanted fragments of surgically removed endometrium in the rhesus monkey, our first experiments were done. These will not be reported in detail since they but reaffirm the work of others.

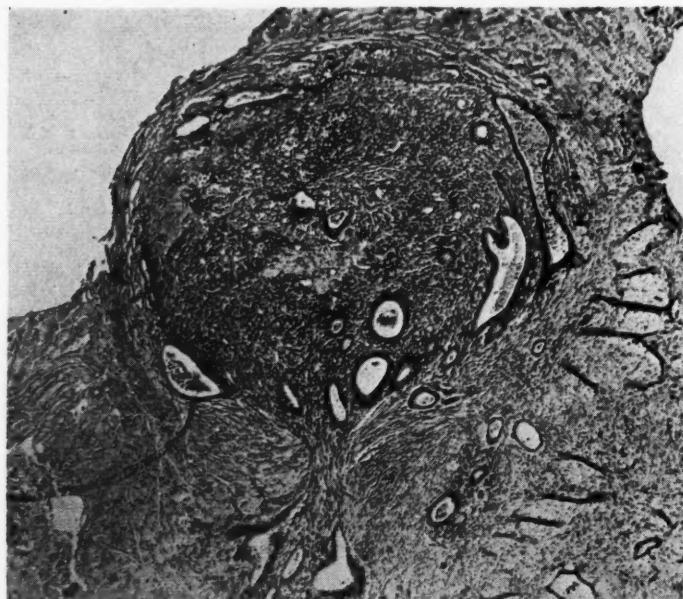


Fig. 3.—Endometriosis in the anterior abdominal wall of monkey No. 880, twenty-six days following endometrial transplantation. ($\times 100$.)

Seven adult monkeys were used for these autologous endometrial transplantation experiments. Five monkeys had been observed for at least three menstrual periods before operation and two monkeys were an estimated 120 to 140 days pregnant at the time of transplantation. The five menstruating monkeys were operated upon on the fourth, fifth, fifteenth, eighteenth, and twenty-third days of the menstrual cycle, respectively. Monkey 852 was given a subcutaneous implantation of 24 mg. of estrone on the seventh day of the cycle and sixteen days before operation. Monkey 869 was given a subcutaneous implantation of 12 mg. of estrone on the fourth day of the cycle and eleven days before operation.

The operative procedure was almost identical in each animal. A longitudinal incision was made in the uterus and the fetuses were removed from the two pregnant animals. The endometrium was excised by knife from the uterine fundus and then cut into fragments 2 to 3 mm. in diameter. These fragments were transplanted to the anterior cul-de-sac, posterior cul-de-sac, rectal wall, broad ligaments, one or both ovaries, cecal wall, and the sides of the abdominal incision. The receiving surface was first scarified by the knife and the transplant was lightly sutured in place at one border by a silk suture. Ovarian transplants were made into the ovarian substance. In two instances minute fragments of endometrium suspended in saline were injected into an ovarian vein while the proximal portion of the vein was compressed.

Microscopically viable transplants with endometrial glands and stroma and adjacent fibrosis were found in at least one area in all but one monkey after

26 to 522 days' observation. In some instances as many as four viable transplants were recovered. At the time of exploratory laparotomy the nodules grossly were small, fibrotic, and raised, with occasional black spots, and only one transplant (an ovarian, 270 days later) showed a brownish-black 4 mm.

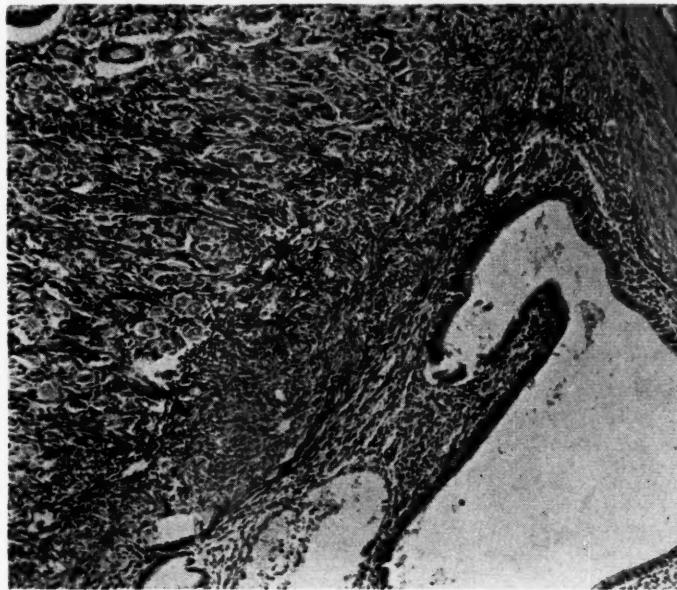


Fig. 4.—Endometriosis in the right ovary of Monkey 882, seventy days after endometrial transplantation. Healthy ovarian tissue with primordial follicles is seen on the left. ($\times 100$.)



Fig. 5.—Area of endometrial stroma and glands in the cecal wall of Monkey 883, two hundred sixty-six days following transplantation of endometrium. ($\times 60$.)

cyst. All of the transplants were not biopsied because of the fear of completely removing them. Figs. 3, 4, and 5 are examples of some of the transplants. One monkey died of extensive abdominal and pulmonary tuberculosis 56 days after

the endometrial transplantation, and it was this animal which showed no viable endometrial tissue. No implanted endometrium could be found attributable to the injection of suspended endometrial particles into the ovarian veins.

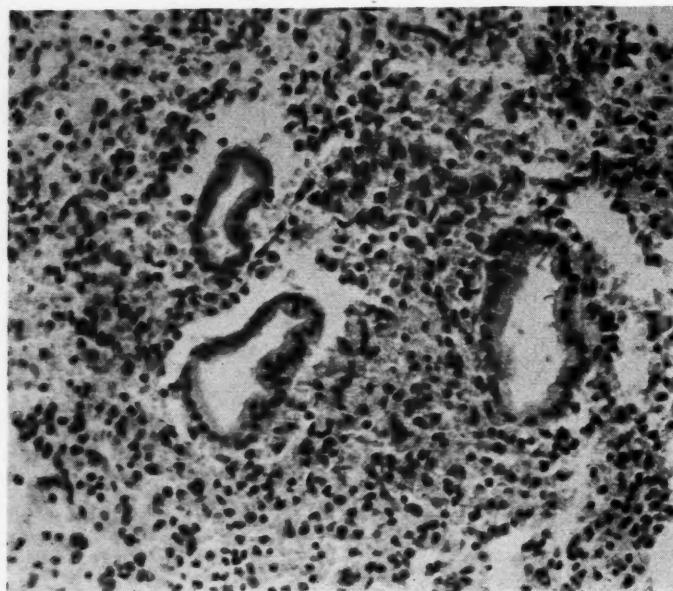


Fig. 6.—Portion of endometrial tissue passed from the vagina at the time of menstruation in a 21-year-old patient. Most of the cells appear histologically viable. ($\times 300$.)

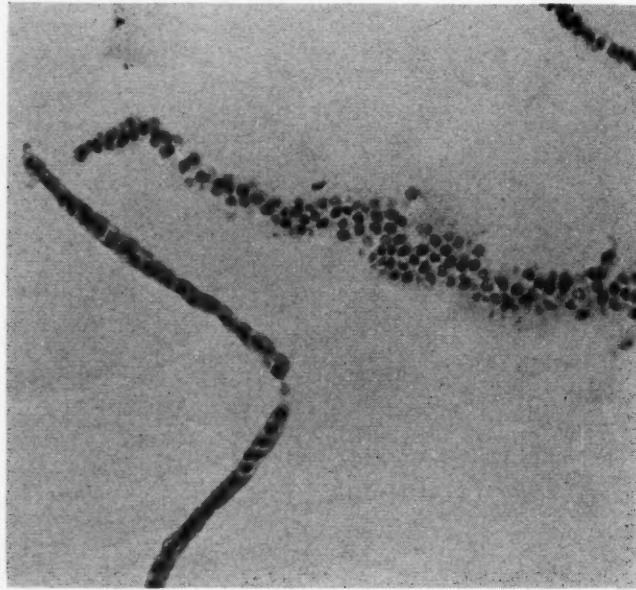


Fig. 7.—Loose fragments of endometrial cells spontaneously passed at the time of menstruation. This is another area in the same case as Fig. 6. ($\times 300$.)

Variability in the number and growth of the transplants could not be correlated in any fashion with the use of postmenstrual, interval, premenstrual, or pregnant endometrium. Preoperative implantation of estrone had no apparent effect.

Two of the monkeys used in these experiments are living and will be followed by periodic rectal examinations and exploratory operations to determine the effect of time and continued menstrual function.

These experiments, simply confirmatory of many previous ones, only prove that nonmenstruating endometrium is capable of growth. They leave completely unanswered the question of the ability of desquamated menstrual endometrium to grow.

Experiments With Desquamated Endometrium

Novak and Te Linde²⁴ in 1924 believed that menstruation was a crumbling, necrotic process, best termed desquamation. They doubted the possibility that the partially autolyzed endometrial fragments occasionally found during the first two days of menstruation would retain sufficient viability to implant themselves, survive and flourish. Cron and Gey²⁵ obtained material from the uterus on the second day "by gently removing with a dull curette" and succeeded in demonstrating activity of the tissue after one month's cultivation in tissue culture. This work has frequently been cited as proof of the viability of menstrual material. However, the use of a dull curette, gentle as it may be, is instrumentation and would very probably have detached particles of glands and

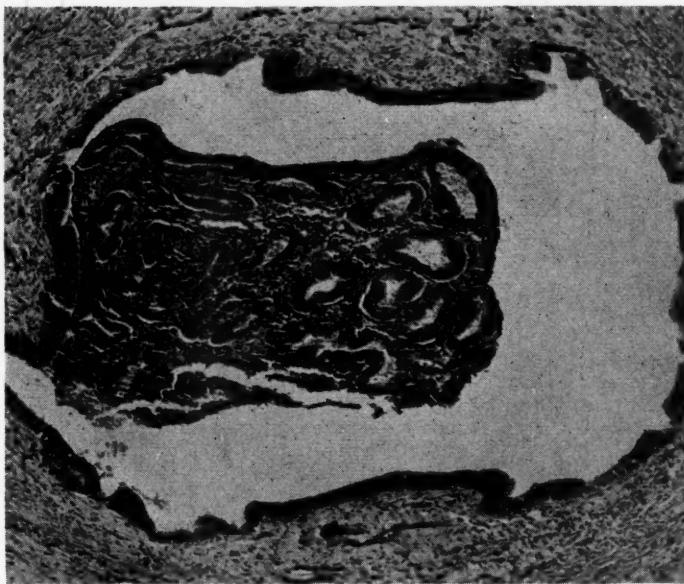


Fig. 8.—Unattached fragment of endometrium found in the isthmic portion of a removed human tube. No external endometriosis was identified in this case. ($\times 100$.)

stroma from the middle and deep portions of the endometrium which ordinarily would not have been cast off. Heim's²⁶ experiments with monkeys have been interpreted as proving that desquamated endometrium cannot live. Heim opened the uterus on the first day of menstruation and scattered the contents throughout the abdomen; 56 days later no endometrial tissue was identified outside the uterus. In another experiment he did a fundectomy on the first day of menstruation, placed the contents in a peritoneal pouch and left the fundus open; 39 days later adhesions had formed, the fundus opening had closed, and no ectopic endometrium was found. In these two experiments viable, deep endometrium was cut across and instrumented so that the real surprise is that he did not find ectopic endometrium subsequently. In addition, the period of

observation was so short that his conclusions do not seem warranted. Heim, in a third experiment, scattered human first-day menstrual discharges into different areas of a monkey's abdominal cavity and 46 days later found no particles of endometrium. Since Greene²⁷ has shown that with the exception of pia arachnoid and sheath of Schwann tissue only embryonic and malignant tissues are capable of growth on heterologous transplantation, the failure of growth in Heim's

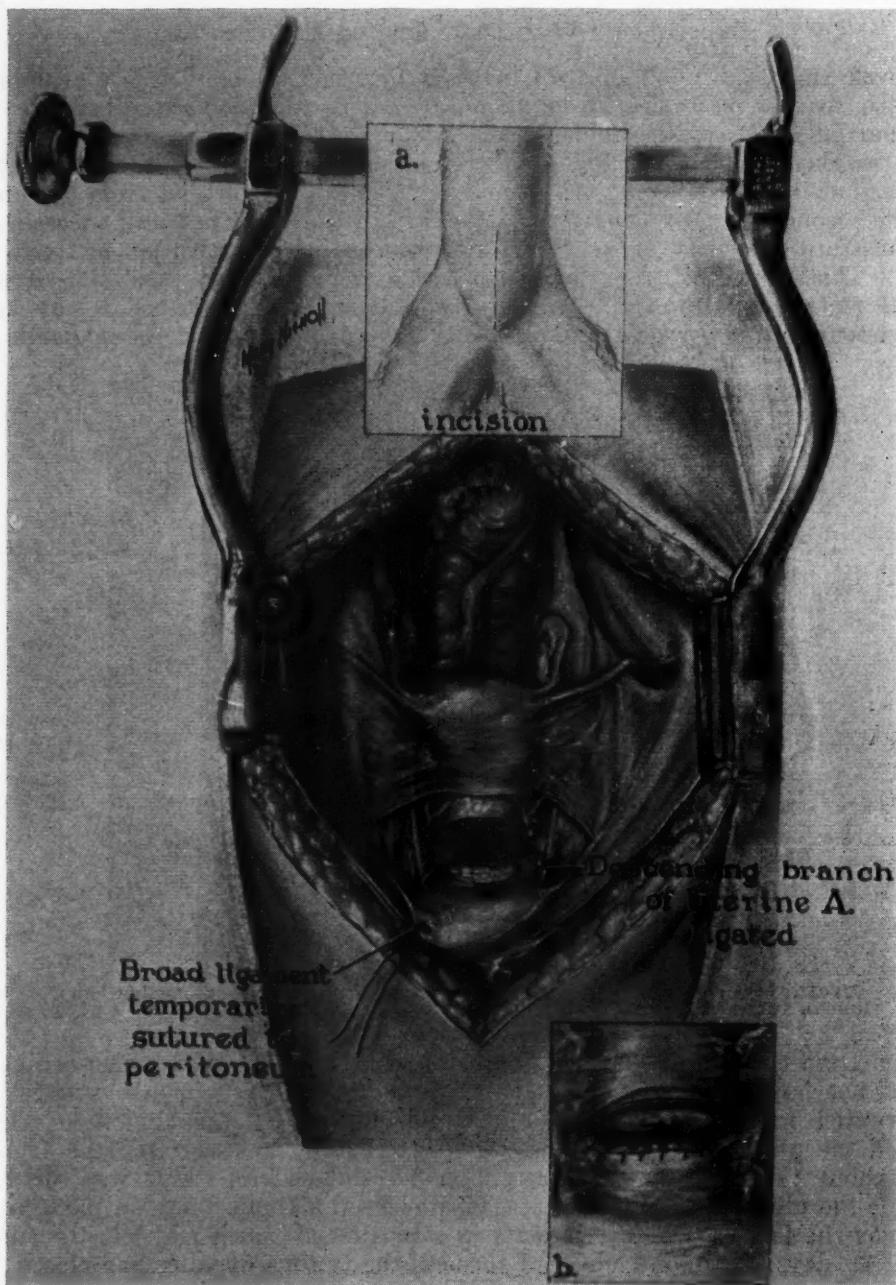


Fig. 9.—First step in the experimental surgical procedure on monkeys to allow intra-abdominal menstruation. The descending branches of the uterine arteries have been divided and tied and the lower portion of the cervix closed and peritonized.

third experiment is not even suggestive evidence. Geist²⁸ drew menstrual blood through a pipette, the diameter of which was one-third the diameter of the interstitial portion of the tube. By supravital staining methods recovered endometrial cells were shown to be viable for at least one hour. Sampson⁴ in four patients operated upon during menstruation stripped the blood from the tubes and by staining found endometrium-like epithelial cells and clumps of cells resembling endometrial stroma. In four other patients operated upon at the time of menstruation, the removed tubes showed apparently healthy fragments of endometrium in the lumen. Watkins²⁹ operated upon eight patients during menstruation. All of these had retrodisplaced uteri and all showed some degree of retrograde bleeding (10 to 60 c.c.). Microscopic examination of this material showed red blood cells, white blood cells, endometrial cells, frequent clumps of debris, and in two cases glandular endometrial cells.

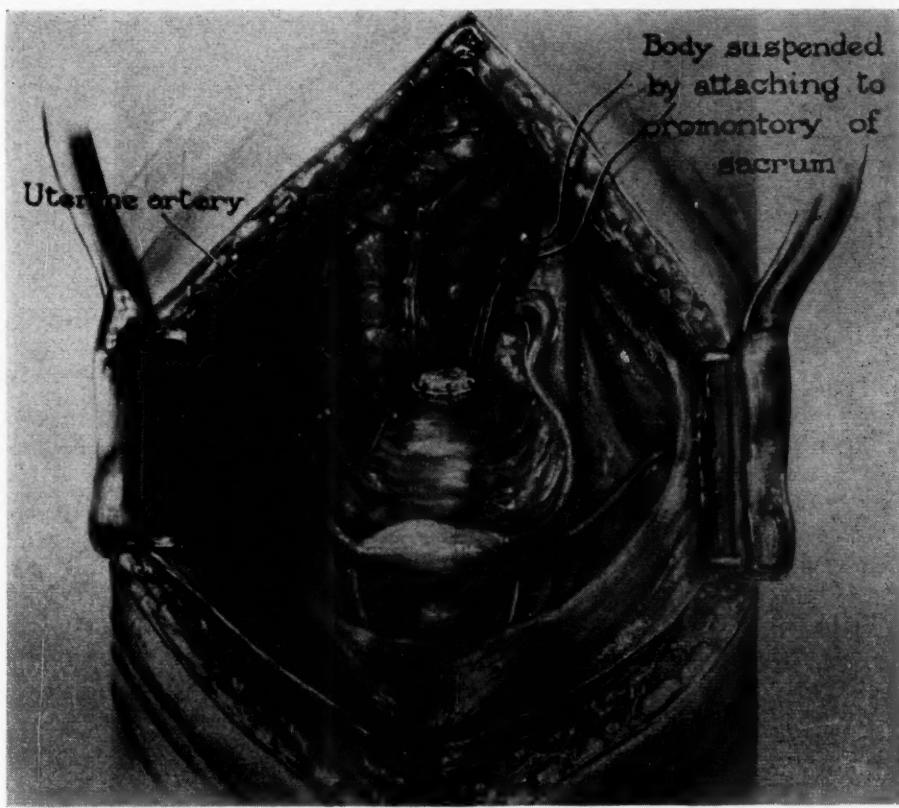


Fig. 10.—Second step in the experimental surgical procedure on monkeys to allow intra-abdominal menstruation. The remaining uterus has been turned through 180 degrees, so that the cervical os points toward the promontory of the sacrum. The location of the fixation suture was varied at its upper attachment.

The authors have had two cases suggesting that viable endometrial tissue can be shed or easily separated from the uterine lining. One case (E. K. Path. No. 80397) was that of a 21-year-old unmarried woman who complained of severe dysmenorrhea since the onset of menstruation and whose pelvic organs were essentially normal. She had frequently passed large fragments. One such fragment which she expelled from the vagina was immediately placed in a preserving fluid. Sections of this material showed large fragments and isolated small groups of what appeared to be histologically viable endometrial epithelial and stroma cells (Figs. 6 and 7).

A second case (W. A. Path. No. 84465) was that of a 29-year-old married woman with repeated attacks of severe right-lower-quadrant abdominal pain before and during menstruation. Two years previously she had the left tube and ovary removed for a dermoid cyst and the right ovary partially resected for a follicle cyst. At operation, done on the twentieth day of the cycle, she was found to have two large, adherent, hemorrhagic cysts of the right ovary. Microscopically these cysts proved to be corpus luteum cysts and there was no suspicion of endometriosis. Just distal to the interstitial portion of the right tube

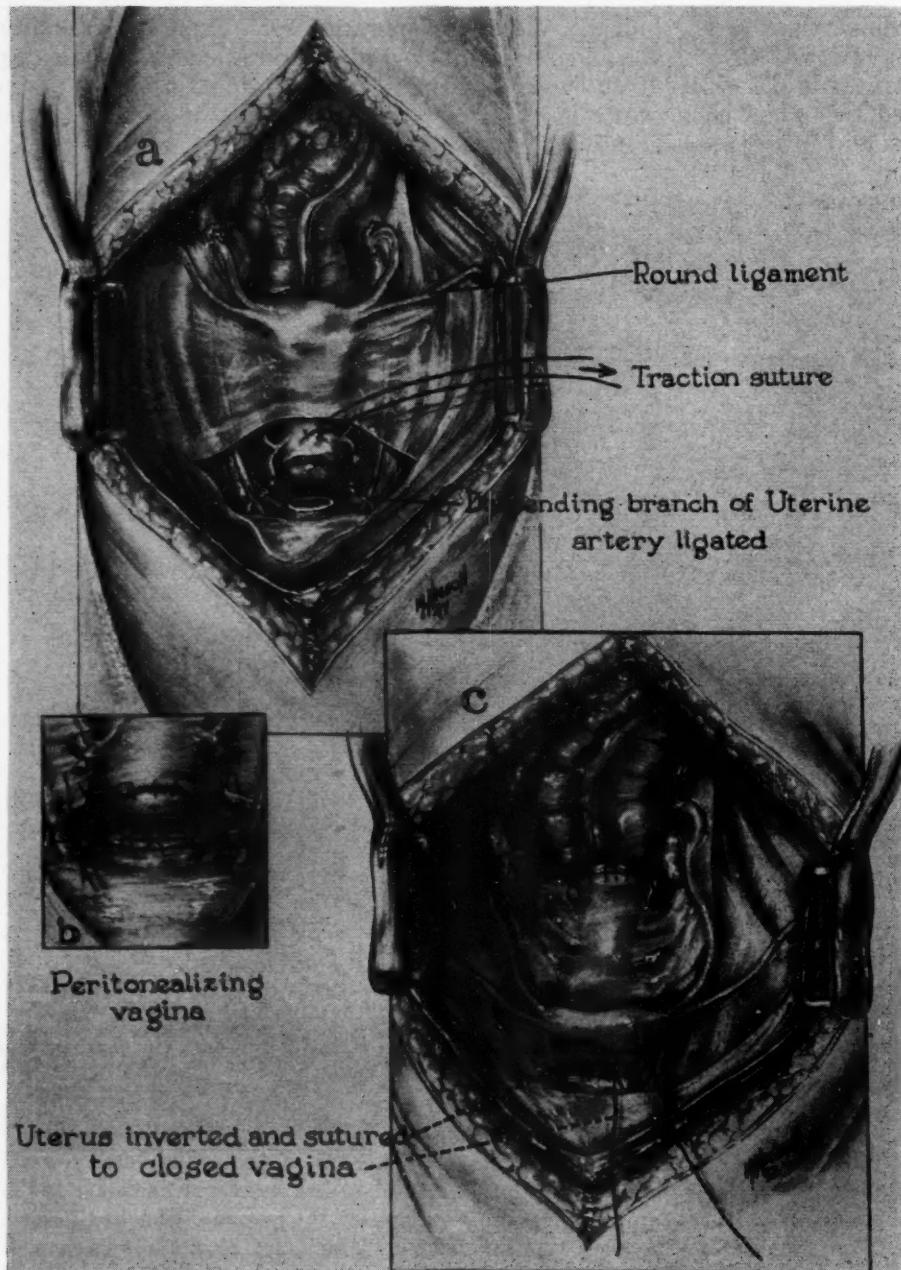


Fig. 11.—The experimental surgical procedure on monkeys to allow intra-abdominal menstruation in which the entire uterus is separated from the vagina and turned through 180 degrees. The lower right fixation suture to the closed vagina was used in only one instance.

a stained section showed a large fragment of endometrial tissue (Fig. 8). Semi-serial sections showed this fragment to be unattached to the tubal epithelium and present through the entire block, a distance of over 2.5 mm. It was also identified over an equal longitudinal distance in another block nearer the cornu of the uterus.

The evidence for and against retrograde tubal menstruation and consequent implantation of endometrial fragments continues to mount, yet the fundamental

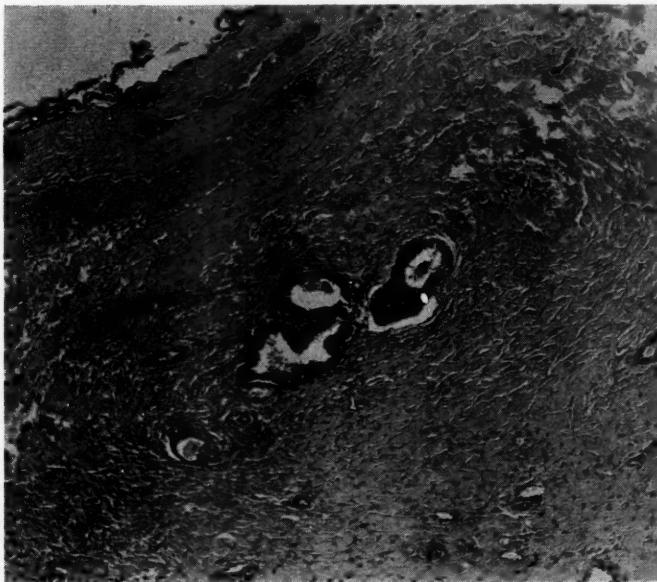


Fig. 12.—Monkey 847. Endometrial glands in the fibrous tissue fixing the bowel wall to the cervix 259 days after reversing menstrual flow. ($\times 100$.)

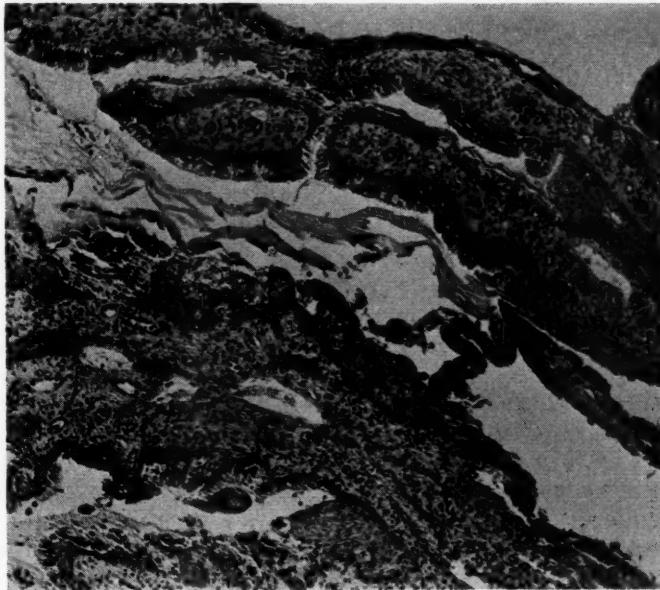


Fig. 13.—Monkey 847. Biopsy of the cervix adherent to bowel 259 days after reversing menstrual flow. This shows endocervical epithelium, squamous metaplasia, and no evidence of endometrial tissue. ($\times 100$.)

question remains unanswered. Histologic viability does not mean physiologic viability and the literature records no uncontested experiment which demonstrates that castoff, desquamated, menstruated endometrium can attach itself, grow, and spread in an ectopic location. The following experiments were done in an effort to answer this very debatable point.

Method I.—

As shown by Clark and Corner,³⁰ the cervix of the rhesus monkey is Z shaped and contains two colliculi, thereby making entrance into the uterus via the vagina extremely difficult. The cervix uteri of the monkey is similar to that of the human infant female in one respect—it comprises about two-thirds of the entire uterus.

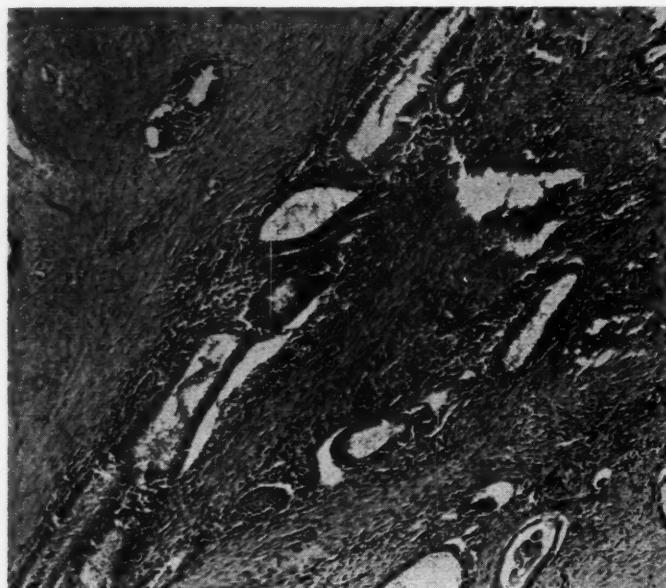


Fig. 14.—Monkey 849. Endometriosis in the tissue between bowel and cervix 963 days after allowing intra-abdominal menstruation. The pigment-laden macrophages are suggestive evidence of menstruation within this area of endometriosis. (X100.)

A method of diverting menstrual flow from its usual vaginal exit in order to permit intra-abdominal menstruation was surgically devised. At laparotomy the descending branches of the uterine arteries were clamped, cut, and tied. The cervix a few millimeters above the vagina, or in some cases the vagina was cut across and the uterus was either turned through 180 degrees or shifted to another position within the abdomen (Figs. 9, 10, and 11). The raw surfaces were peritonized and the lower cervical stump or vagina was closed and peritonized. These procedures were all done at approximately the midinterval in the menstrual cycle, the uterus was gently handled, and the blood supply to the uterus and ovaries carefully preserved. At no time was endometrium instrumented in any way. In all cases in which the cervix was cut across, the incision was made very close to the vagina and a biopsy of the proximal cervical canal revealed only endocervical tissue. Ten monkeys were altered in the above fashion and five of these subsequently developed endometriosis. Because we believe that the details of these experiments are important to the critical experimenter, a short history of these monkeys is given below.

Monkey 847: A detachment of the entire uterus with a twisting of the uterus through 180 degrees was done on May 20, 1947. There was slight bleeding from the vagina 258

days after operation and the following day an exploratory operation was done. Extensive adhesions were found in the pelvis and the rectosigmoid bowel was firmly bound to the cervix by a thick zone of fibrous tissue. The bowel wall and microscopic study of the fibrous tissue adherent to the bowel revealed 3 endometrial glands (Fig. 12). A biopsy

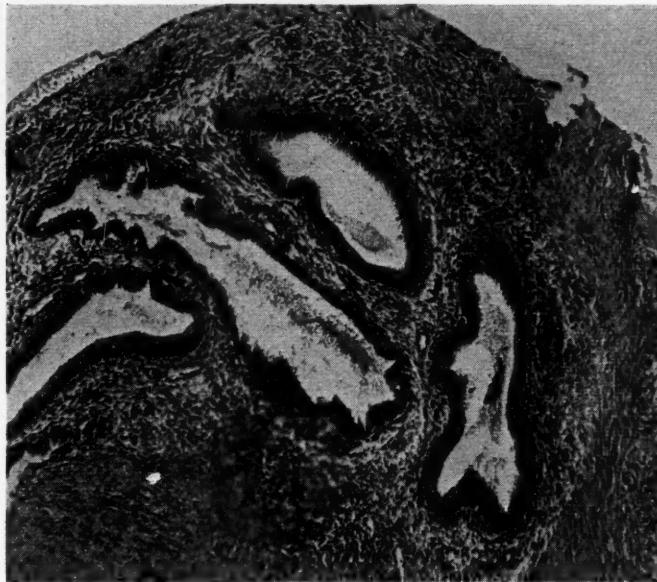


Fig. 15.—Monkey 872. Endometrial glands and stroma grossly appearing as a purplish area on the right lateral pelvic wall 404 days after the uterus was turned through 180 degrees. This was one of several such areas at some distance from the reversed cervix. ($\times 100$.)

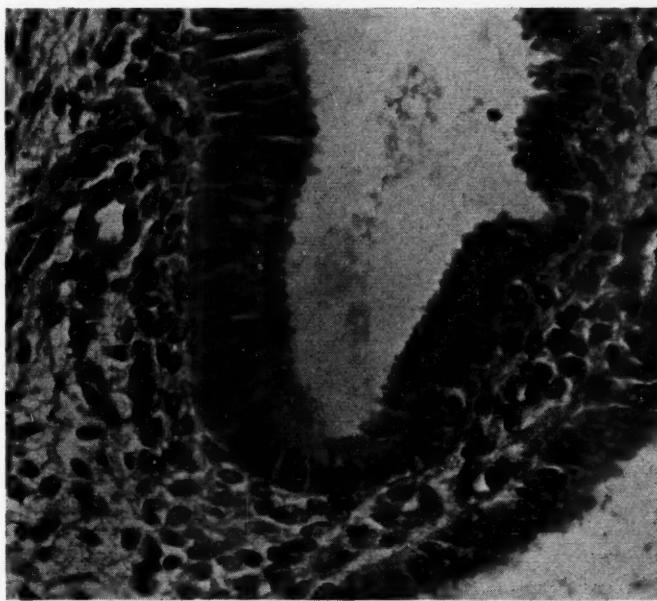


Fig. 16.—Monkey 872. High-power study of an area in Fig. 15, to show the characteristic epithelium and stroma. ($\times 500$.)

taken from the cervical os showed endocervical tissue with squamous metaplasia (Fig. 13). This monkey died 89 days later of dysentery and no other areas of endometriosis were found.



Fig. 17.—Monkey 872. Operating table appearance of the adherent bowel and puckered scarring (indicated by pointer) on the left side of the lower abdomen 739 days after menstrual flow was reversed. Biopsies of this area revealed endometriosis of a more active nature than would be suspected by the gross appearance.



Fig. 18.—Monkey 872. Operating table appearance of the adherent bowel and purplish-red nodules and streaks (below pointer) on the right side of the lower abdomen 739 days after the reversing of menstrual flow. Biopsies showed these to be nodules of every active endometriosis.

Monkey 840: On Feb. 26, 1947, the uterus was turned after being cut across a few millimeters above the vagina. Exploratory operations were done 160 and 335 days later. Extensive adhesions were found and in the latter instance a few suspicious endometrial glands were found in the adherent rectosigmoid fibrous tissue. After 963 days endometrial glands and stroma were very prominent in this adherent tissue (Fig. 14). The monkey died of intestinal obstruction due to an adherent volvulus 1,007 days after the original operation. In these 1,007 days it had on 9 occasions spotted bloody material from the vagina for one to four days. At autopsy, in addition to the adherent, twisted loop of sigmoid bowel and extensive adhesions, a cervicorectal communication had formed. Areas of endometriosis surrounded the uterus and one long channel could be probed in these areas which communicated with the side of the vagina. This explained the vaginal bleeding. It was interesting that the small cervical stump within the vagina had completely atrophied. Also worthy of note was the fact that one ovary was buried between the rectum and fundus, but had developing follicles and a recent corpus luteum.

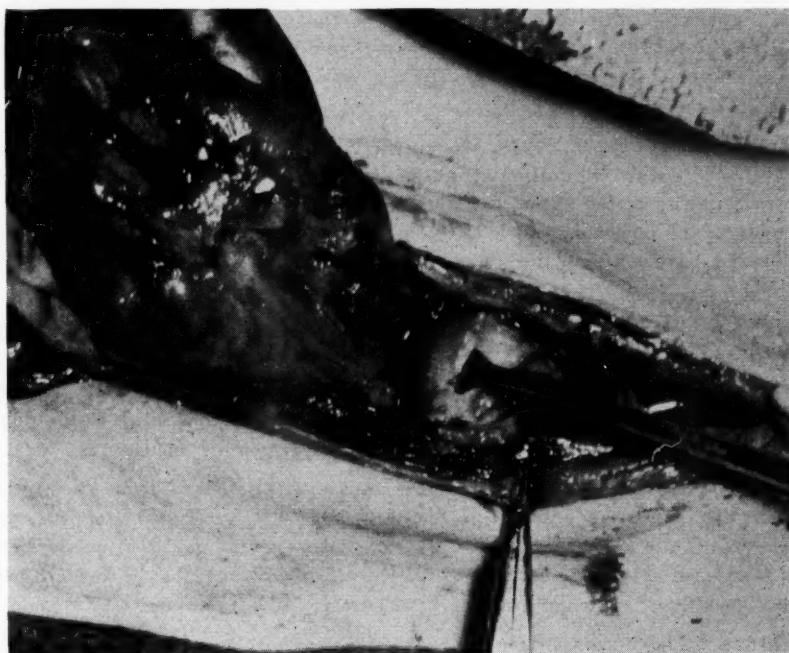


Fig. 19.—Monkey 889. Gross appearance of the separated bowel 241 days after the uterus was reversed to allow intra-abdominal menstruation. The mucosa clip is on the reversed cervix, and the thickened, whitish area on the adjacent bowel contained endometrial glands and stroma.

Monkey 872: On Nov. 13, 1947, the uterus except for a small fragment of distal cervix was turned through 180 degrees. Seventy-five days later extensive adhesions of the bowel and cervix were found and in the fibrous tissue over the adherent bowel one questionable endometrial gland was seen microscopically. Four hundred four days after the original procedure exploration of the abdomen again showed the adhesions of bowel and cervix as well as bowel to bowel in the pelvis. Several centimeters above the cervix on the bowel wall and also rather far on the right lateral pelvic wall were tiny purplish spots. These were all biopsied and they showed (Figs. 15 and 16) definite endometriosis, as did the fibrous tissue on the adherent bowel. Findings at exploratory laparotomy on the 739th day after operation are represented by Figs. 17 and 18. This monkey has had slight vaginal bleedings on four occasions.

Monkey 887: A low amputation across the cervix was done on Dec. 3, 1948, and the uterus was turned through 180 degrees. The characteristic rectosigmoid adhesions were again found 172 and 297 days after the original operation, but only on the latter occasion was endometriosis found in the intervening tissue. This animal had slight vaginal bleeding on only one occasion after operation.

Monkey 889: A low amputation across the cervix was done on Jan. 21, 1949, and the uterus turned through only 90 degrees, so that the cervix pointed ventralward. One hundred eighty-five and 241 days later, endometrial glands and stroma were found in the fibrous tissue between the bowel and the cervix. The gross appearance of the separated bowel and cervix is shown in Fig. 19.

The following five monkeys were similarly operated upon, but gross and microscopic endometriosis did not develop:

Monkey 850: The complete uterus was detached from the vagina and turned through 180 degrees on Feb. 26, 1947. By rectal examination the uterus became markedly enlarged and softened, so that 99 days later exploration of the abdomen was planned. The animal died while being anesthetized, and the autopsy revealed a large hematometra. There was no evidence of endometriosis microscopically. It was interesting that the tubes in this case were normal in appearance.

Monkey 866: On Feb. 26, 1948, the cervix was cut across just above the vagina and the uterus was not turned but allowed to point into the anterior cul-de-sac by fixing the tip of the cervix lightly to the anterior abdominal wall. At this operation several tiny whitish spots were seen on the omentum which by biopsy proved to be tuberculosis. This monkey died 133 days later of extensive tuberculosis and no endometriosis was found.

Monkey 896: The uterus was completely detached from the vagina on April 29, 1949, and the cervix suspended to the anterior abdominal wall, so that it would discharge its menstrual material into the anterior cul-de-sac. One hundred fifty-one days later the animal was explored and a clean, direct, cervicosigmoidal fistula was encountered. There was no fibrosis about the fistula and endometriosis was not encountered by biopsy. The sigmoid opening was repaired, but the animal died 6 days later of peritonitis.

Monkey 898: On Feb. 18, 1949, the entire uterus was detached from the vagina, turned through 90 degrees, and the cervix lightly sutured to the anterior abdominal wall. The uterus increased in size upon rectal examination and the animal died while being given intravenous Nembutal 214 days after operation. Autopsy revealed a hematocervix, with minimal hematometra and no hematosalpinges. There were no adhesions.

Monkey 874: The lower portion of the cervix was cut across on March 11, 1948, and the cervix was shifted and lightly sutured into the right posterior cul-de-sac. The monkey rapidly lost weight, but ate ravenously. She became known as "Miss Bones." Two hundred eleven days after operation the abdomen was opened and a right hydronephrosis and hydro-ureter down to the displaced cervix were found. Subsequently the animal gained and when explored 449 days from the original procedure was found to have an hematocervix. This hematocervix was opened very low down on the cervix and 137 days later a cervicorectal fistula had formed. The rectal fistula was repaired and the animal continues to do well. No endometriosis was found on any of the three explorations. It may be eventually discovered that endometriosis was responsible for the ureteral blockage. The authors are more inclined to ascribe the complications to poor surgical technique.

To summarize Method I, ten monkeys were surgically altered in order to permit intra-abdominal menstruation. Five of the animals 75 to 963 days following the alteration developed extensive adhesions in the pelvis and endometriosis was microscopically found in the fibrous tissue between the bowel and the cervix. One monkey developed characteristic gross and microscopic endo-

metriosis on the bowel wall and the pelvic peritoneum at some distance from the cervix. Four of these five monkeys had one to four days of slight vaginal bleeding after the alteration and in one instance a fistulous tract was found extending from the area of pelvic endometriosis to the side of the vagina. The uteri and ovaries appeared to maintain their function, perverted though it was. Five monkeys failed to develop microscopically proved endometriosis, and these showed a single one or combinations of the following: hematometra, hemato-cervix, cervicointestinal fistula, hydroureter and hydronephrosis, peritonitis, and extensive tuberculosis.

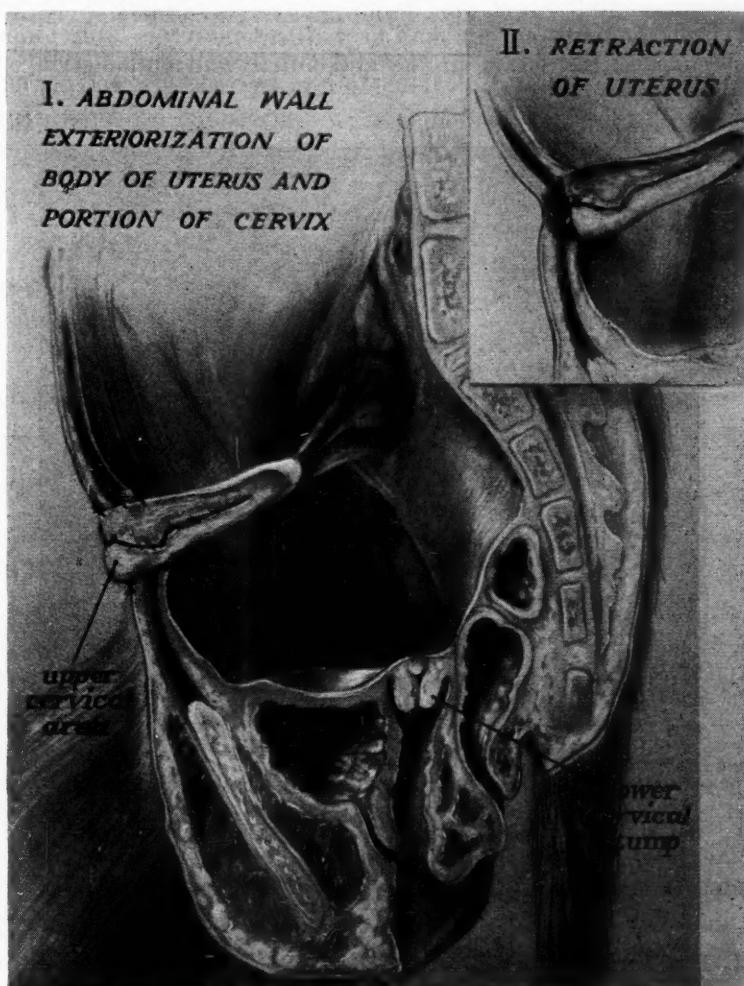


Fig. 20.—Drawing of the operative procedure on Monkey 875. The uterus except for the distal portion of the cervix was brought out through the anterior abdominal wall. The insert shows the retraction of the uterus and the scarring in the anterior abdominal wall.

Method II.—

It was hoped that a method could be devised whereby Rubin's tests could be easily performed at the time of menstruation. The Z-shaped cervix and the lack of available parous animals were a handicap. In one instance the following was attempted.

Monkey 875: On Dec. 18, 1947, the descending uterine vessels were clamped, cut, and tied and the cervix was cut across at about its mid-portion. The upper cervix was then brought out through the abdominal wall and sutured in place (Fig. 20). A biopsy of the proximal cervix above the level of the incision showed endocervical tissue. Within two months the cervix had retracted back into the abdomen and the procedure was considered a miserable failure. One year after the original operation the monkey was explored. Biopsies of the scar tissue along the line of retraction in the anterior abdominal wall revealed endometrial glands and stroma (Fig. 21), and a biopsy of the cervix showed endocervix with slight squamous metaplasia. The ovaries appeared normal.

To summarize Method II, one monkey was so altered as to permit it to menstruate into the anterior abdominal wall. One year later along the scar tissue of the line of retraction in the abdominal wall endometrial stroma and glands were proved to be present.

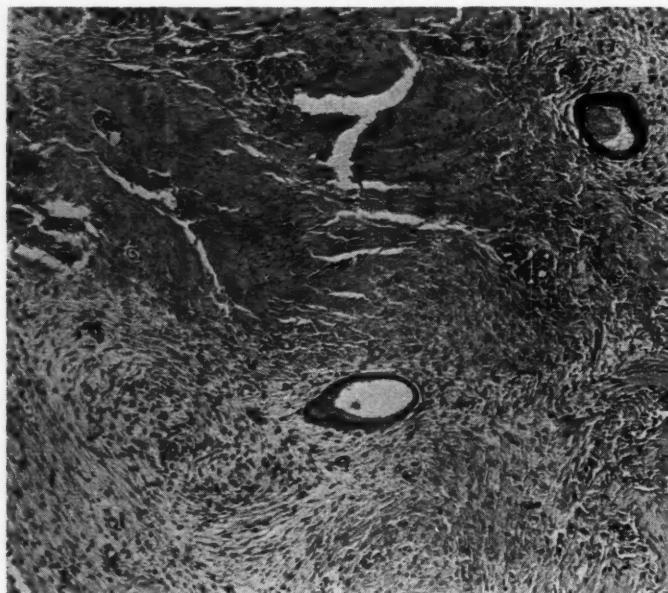


Fig. 21.—Monkey 875. Endometrial glands and stroma in the scar tissue along the line of uterine retraction, 364 days after the surgical procedure in Fig. 20. (x100.)

Comment

The experiments on the rhesus monkeys were done with particular care to avoid instrumenting or in any way traumatizing the intact endometrium. The cervix of the monkey comprises approximately two-thirds of the total longitudinal distance of the entire uterus. When the cervix was cut preliminary to reversing the direction of menstrual flow, the cutting was done just above the vagina and in each instance a biopsy of the proximal portion was conclusive that endocervix and not endometrium was incised. One monkey whose entire uterus was reversed (i.e., the incision was across the vagina) developed endometriosis. The ovarian and uterine blood supply were not impaired, since subsequent ovarian biopsies showed essentially normal histology and the uterus did not atrophy in any instance. The evidence that the altered uterus men-

structed is fairly definite—the blood supply was preserved and four of the five monkeys which developed endometriosis bled vaginally on one to nine occasions. One of the animals which had vaginal bleeding following operation was found at autopsy to have a fistulous communication between the area of the external endometriosis and the side of the vagina.

Aside from the possibility that menstruating endometrium may have been shown to be viable, other explanations were considered. We believe that they can be excluded. A heteroplasia of endocervical to endometrial tissue or direct extension of endometrium from the fundus of the uterus into the peritoneal cavity were excluded by the following fact. The portion of the cervix adjacent to the adherent bowel was freed and extensively biopsied in every case. Normal endocervical tissue or endocervix with squamous metaplasia was consistently encountered in these biopsies. A third possibility, heteroplasia of the pelvic peritoneum secondary to the operative and blood irritation, cannot be disproved. This seems unlikely since in the transplantation experiments using basal endometrium no areas of endometriosis developed as a result of trauma and spilled blood except at the sites of transplantation. Venous or lymphatic dissemination is mentioned only to be ruled out by the evident gross and microscopic studies.

These experiments are indicative proof that in the adult female monkey, castoff menstrual endometrium is viable and capable of growing to produce lesions in the pelvic area similar to the lesions found in human endometriosis.

Summary

1. Some of the previous laboratory experiments and clinical data are reviewed and criticized.
2. Histogenetically there are at least two primary and essential debatable questions. The first: Is castoff endometrium dead and incapable of growing or is it viable? The second: Can this endometrium in sufficiently large particles pass in a retrograde fashion through the tubes and into the peritoneal cavity? The first question is experimentally considered in the present studies.
3. The *Macacus rhesus* female monkey was chosen for these experiments because of its menstrual pattern, so similar to that of the human female, and since there is at least one instance of spontaneous endometriosis in this animal.
4. Endometrium incised from the uterine lining was autogenously transplanted throughout the pelvic organs, intestines, and abdominal wall in seven monkeys. Six of these animals developed at least one "take." The time of transplantation relative to the day in the menstrual cycle or pregnancy did not appear to affect the development of the transplants. Preoperative implantation of estrone pellets in two instances had no apparent effect.
5. Two cases in human beings are cited which indicated that histologically viable endometrium may appear in vaginal menstrual discharge or in the tubes.
6. Ten monkeys were surgically treated to permit them to menstruate into the abdominal cavity. In no instance was intact endometrium instrumented or traumatized. Five monkeys developed extensive adhesions of the bowel to the

turned cervix and the intervening fibrous tissue revealed endometrial tissue. One of these five animals also developed typical endometriosis lesions on the bowel wall and pelvic peritoneum at some distance from the turned cervix. Five of the surgically altered monkeys failed to develop external endometriosis, but had numerous complications secondary to either the type of operation or infections.

7. One monkey was so surgically altered that it menstruated via the cervical canal into the anterior abdominal wall, and subsequently developed endometriosis in the abdominal wall scar tissue.

8. Heteroplasia of the pelvic peritoneum or endocervix, direct extensions from the intact endometrium, and venous or lymphatic spread are not considered feasible explanations from the gross and microscopic studies.

9. These experiments are believed to be strongly indicative of the fact that at least some portion of menstrual castoff endometrium is viable.

This work was done under an American Cancer Society grant recommended by the Committee on Growth of the National Research Council. The Abbott Laboratories generously supplied the estrone used for subcutaneous implantation. This work would not have been possible without the kindness, encouragement, and active assistance of Dr. George W. Corner and his staff of the Department of Embryology of the Carnegie Institution of Washington. Dr. Robert Faulconer and Dr. Edwin I. Smith gave invaluable assistance in the animal operating room.

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Discussion

DR. EDWARD ALLEN, Chicago, Ill.—Drs. Te Linde and Scott have just presented the first major experimental study of endometriosis in a menstruating animal since Sampson's epoch-making clinical work on the human being in 1921. I appreciate this opportunity to be the first officially to congratulate them and to discuss their results before this Society. The preliminary confirmation of work by previous investigators by implantation of excised endometrium in the first seven nonpregnant and pregnant monkeys is characteristic of the authors' previous painstaking contributions to gynecologic literature.

The previous report of the senior author working with Hartman does not state what percentage of their animals developed endometriosis except to say that numerous instances were found two to four years later in 56 animals subjected to 99 hysterotomies. Most of these monkeys were pregnant. At least in the human being we have thought that endometriosis was relatively more frequent following operations upon the pregnant uterus than on the nonpregnant organ. The authors did not find this to be so in this experiment.

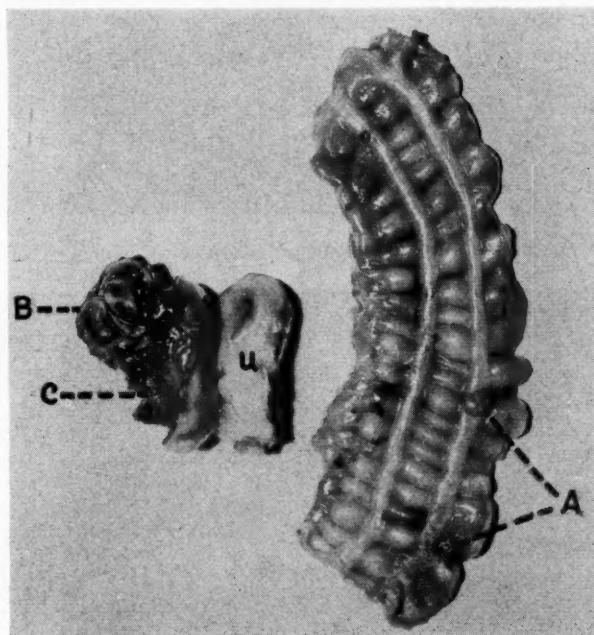


Fig. 1.—A, Ovary. B, Adenoma, rectovaginal septum. C, Uterine wall, "U."

The presence of endometriosis in one-half of the nonpregnant animals in the second series just reported is very exciting. It seems to substantiate their thesis that desquamated endometrium is viable and capable of implantation and growth. Also, at long last, we now have a method which will permit us to study endometriosis in all of its various phases. The operative procedure is a very ingenious way of making an internal os out of an external os. The careful histologic examination of the transected area of the cervix indicated that endometrium was not exposed by this procedure. It is noteworthy, however, that in all but one of these animals the endometrial lesions occurred immediately around the new external os. Is this final proof that this area was the settling basin for the bits of endometrium which flowed from the cut cervical canal, and that the one instance in which the lesions were far distant on the bowel wall and peritoneum meant only a greater overflow? Or can this be another example of metaplasia of exposed cervical epithelium growing in a new environment similar to that suggested by the authors in Monkeys 847 and 875, or the squamous metaplasia described by Sampson for tubal epithelium in am-



Fig. 2.—Adenomyosis of the uterine wall.



Fig. 3.—A, Endometrial lesion, rectosigmoid. B, Bowel lumen.

putated tubal stumps? We have not found endometriosis near the transplanted cervical os in any of our animals. I rather doubt that this is metaplasia because endometriosis in the human cervix is very rare. However, I should like to show you a few slides from one of our monkeys which have made us pause in this conclusion.

These slides are taken from one of our animals in which the cervix had been freed from its attachments with minimal trauma in a manner similar to that used by the authors and transplanted without transection just beneath the rectus fascia of the abdominal wall. A Rubin test was attempted on this animal before the cervix was buried in the abdominal tissues. This procedure effectively blocks entry of the menstrual blood to the peritoneal cavity except by way of the tubes or, as Sampson has suggested, by way of blood or lymph vessels. This monkey eventually developed a widespread endometriosis which had all of the characteristics of that found in the human being.



Fig. 4.—Adenoma, rectovaginal septum. A, Gland area far distant from cervix lined by high columnar mucus-secreting epithelium characteristic of the endocervix. B, Lined by epithelium typical of endometrium-like tissue.

This is a picture of the organs as they were removed from this animal (Fig. 1). The two endometrial lesions are quite evident on the wall of the rectosigmoid which was resected and successfully reunited by end-to-end anastomosis. The large adenomyoma of the rectovaginal septum is visible just beneath the ovary which grossly resembled a chocolate cyst. Sections from this ovary were suggestive but not characteristic for endometriosis. The cut uterine wall is thicker than normal due probably to the adenomyosis scattered throughout it.

Fig. 2 shows this adenomyosis which was everywhere quite pronounced.

Fig. 3 is taken through the endometrial lesion on the rectosigmoid. The second one was puckered and extended even more deeply into the musculature of the bowel.

Figs. 4 and 5, I believe, are the most important ones for the discussion of the authors' results. Fig. 4 is taken from the large adenomyoma of the rectovaginal septum. This

area is distant from the wall of the cervix, the external os, and near the peritoneum. At first glance it is a typical area for clinical adenomyosis.

Fig. 5 is a higher magnification of one of the glands in the previous slide. It seems to be a continuous gland, the epithelium of which suggests a gradual metaplasia from one type of epithelium to another or possibly a metaplasia from a single source in two directions. The end nearest the cervix is lined by typical endometrial epithelium and surrounded by a fair amount of stroma. This epithelium appears to change as we pass toward the peritoneum, and its outer lumen is lined by high columnar mucus-secreting basal nuclear epithelium rather characteristic for the endocervix.

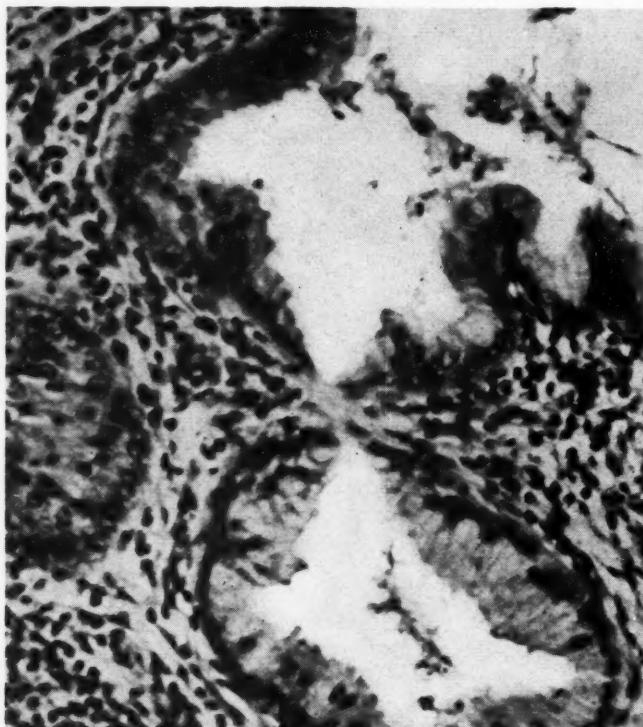


Fig. 5.—Higher magnification of area A in Fig. 4 showing metaplastic (?) epithelium.

The lesions in our monkeys were very slow in developing. Preliminary implantation of the cervix as described was done March 17, 1945. Two succeeding exploratory laparotomies at widely spaced intervals did not reveal definite lesions. Laparotomy done March 2, 1949, revealed multiple lesions from which the photomicrographs were taken. I notice that the element of time has also seemed to be of importance in the authors' monkeys. Those animals dying soon after preliminary operation did not reveal evidence of endometriosis. One might conjecture that, if even small bits of viable endometrium were extruded and implanted during this period, one might find at least small lesions following the first few menstrual periods. Or may it be, as the authors have suggested, that considerable time is required for sensitization by the menstrual blood for implantation or metaplasia of local celomic cells? The carefully transplanted surgical specimens of the first series did not all survive. Endometriosis becomes progressively more frequent in the human female as age advances.

There can be no question that the procedures reported have actually produced endometriosis in some other way than by the usual methods used in transplantation. Endometriosis occurring in 5 out of 10 animals is too frequent for it to be otherwise. Sixty-six

per cent of our animals developed endometriosis. Dr. George Bartelmez tells me that in at least 500 carefully studied monkeys in their series, endometriosis was found only one time. I have seen the slides made from this monkey's tissues; the lesions were so profound and extensive that they finally produced death. Dr. Bartelmez and his co-worker, Dr. Heinrich Kluver, have given me permission to speak of this, although they have not formally reported it.

DR. EMIL NOVAK, Baltimore, Md.—One of the most pleasant memories of my own professional life is the series of very friendly debates before this Society, running over a good many years, with my good friend, the late lamented John Sampson, all dealing with endometriosis, and especially with its etiology. The last paper which Sampson presented before the Society dealt with the metaplastic formation of endometrium from the endosalpinx of tubal stumps, and I remarked at that time that by thus demonstrating the importance of the metaplastic factor he was playing into our hands, and that if we kept on discussing the subject we could probably write a joint paper on the differing etiology of endometriosis, showing that both the metaplastic and the implantation factors must be invoked in the explanation of the origin of endometriosis. For example, I believe that the former is the only tenable explanation of endometriosis in the umbilicus, while no one can deny that implantation may play a possible role in the origin or propagation of pelvic endometriosis.

Dr. Te Linde emphasized the long period of time, in some cases nearly three years, required for the development of the pelvic endometrium in these monkeys. This, at once, it seems to me, must raise the question of whether the endometrium has been transplanted from the uterus, or whether it is the result of metaplastic change incited by the long-continued and recurring irritation produced by the recurring discharge of menstrual blood into the pelvic cavity. One does not need to be a die-hard to raise this point.

The metaplasia theory is based on the concept that areas in the celomic pelvic peritoneum are capable of producing endometrium in accordance with the well-established potentialities of celomic epithelium in general. But the mere presence of these pelvic celomic areas cannot explain endometriosis. Some inciting factor must arise, whether inflammatory, as Meyer believed, or hormonal, as others have suggested. What I am trying to suggest is that the experimental endometriosis produced by Te Linde and Scott may represent implantation, but it can just as readily be explained by metaplasia incited by the prolonged irritation of menstrual blood. I have not discussed this point with Dr. Te Linde, but it seems to me that this question could be settled by prolonged injection into the pelvis of blood, preferably of course menstrual blood, with its probably irritating toxic constituents.

A still-unanswered clinical consideration is the incidence of tubal regurgitation of menstrual blood, on the basis of operations performed during menstruation. It undoubtedly occurs, but my own observations make me think it too uncommon to explain the great frequency of endometriosis. This study is a valuable contribution, but even if it ultimately establishes the implantability of desquamated menstrual endometrium, I believe that most of us will still feel that the mechanism of production of endometriosis cannot always be the same.

DR. JOHN I. BREWER, Chicago, Ill.—Te Linde and Scott do not contend that there is only one theory of origin of endometriosis. They have attempted to show that fragments of endometrium are viable. I would accept their work as demonstrating that this is true.

One bit of information not included in this paper is that offered by Bartelmez. He described some bits of desquamated endometrium under the regenerating surface epithelium of the uterus in a human being which renewed their growth and took part in the regeneration of that endometrium in a normally menstruating woman. I give that as a suggestive bit of evidence that fits with the authors' demonstration very well.

Transference of work such as this in monkeys to the human being always poses a question but it seems that one could interpret that in the human the findings might be similar to those in the Macacus. It has been demonstrated that the endometrium acts in practically all ways just as it does in the human being.

DR. C. FREDERIC FLUHMAN, San Francisco, Calif.—This beautifully executed piece of experimental work is certainly an outstanding contribution to the subject. It has been emphasized that growth of the endometrium in these conditions results from desquamated endometrium at the time of menstruation. I should like to ask Dr. Te Linde if he would comment on what assurance he has that, if the growths are due to endometrial tissue and not metaplastic changes, these were bits of endometrium desquamated at the time of menstruation. It seems to me that small clumps or even isolated cells could find their way from the uterus and out through the cervix during other stages than the menstrual cycle.

DR. JOHN FALLON, Worcester, Mass.—This presentation of Dr. Te Linde's is no academic exercise but the key experiment which interlocks previous observations and experiments to establish the possibility of the tubal reflux theory.

For some years I have worked with endometriosis in monkeys and have kept in touch with Te Linde and Scott's work, so I am grateful for this chance to hear more and for the opportunity you afford a general surgeon to come before you with his monkey business. Of course this key point—the viability of menstruated endometrium—is one of the things I have tried to determine. Using other techniques I have failed, but other observations convinced me that some day the point would be proved: observations such as that of takes without preliminary trauma to the peritoneum and that of propagation of new generations of endometriosis from chocolate cyst contents.

It happens, however, that just when Te Linde and Scott have shown tubal reflux to be possible, I have some evidence in patients that it, or a closely allied mechanism, actually does operate. A map was made of the distribution of small lesions in 138 patients by spotting the lesions of each case on a transparency, then piling the transparencies. Spot maps, of course, furnish only circumstantial evidence. Furthermore, because unusually precise records are needed to justify spotting and because a spot cannot honestly represent a large lesion, the cases upon which these maps are based are nonconsecutive (138 of 430). We cannot evaluate these limitations in three minutes, but I believe that they only limit, do not nullify, the study's value.

The spot map shows concentrations in dependent areas and over little projecting shelves, such as the uterine artery and uterosacral ligament. This pattern would be explained by gravity but not by embryonic rests, metaplasia, lymphatic or vascular distribution.

The pattern points to either tube or ovary as the source of the causing agent.

The pattern persists in the 68 patients of the series who had no demonstrated endometriosis in the ovary. It therefore points to the tube.

These maps contain no evidence for or against any one of the theories of tubal origin. Being based upon nonconsecutive material, they are not evidence against any nontubal theory which might have operated in unmapped cases.

They are circumstantial evidence that, in these 138 patients, the source of endometriosis was the tube.

DR. ROGER SCOTT, Baltimore, Md.—I would like to answer one of Dr. Allen's questions and that is the case of these monkeys not having endometriosis at some distance from the reversed cervix. In one animal (872), we found the lesions were at a considerable distance from the reversed cervix and this was grossly the most characteristic of all the lesions.

As to the proof that menstruation continued, most of the animals had some periodic spotting of blood. One animal was autopsied and we found a direct communication from the endometriosis down to the side of the vagina and blood was coming directly from these areas of endometriosis.

Dr. Te Linde and I tended to believe more in the metaplasia theory than Sampson's theory, and we set out to show that desquamated epithelium would not grow. Since our work has indicated the opposite, we have modified our beliefs by our own experiments.

If you are interested in working with monkeys, you will find that they are very discouraging animals with which to work. They die very easily, particularly of dysentery which is almost universally fatal for this animal. They also develop tuberculosis easily and not infrequently have brawls in which they fall to the bottom of the cage and fracture their skulls. So our work was accomplished with some difficulty and if you are going into "monkey work" you should realize ahead of time that such difficulties will be confronted.

DR. TE LINDE (Closing).—I will say very little because I feel that those who are interested will read the article when it is published and it will stand or fall on its own merit.

In work of this sort every loophole should be sought for. We have tried to anticipate some.

I thank Dr. Novak for his suggestion and we will act on it. We will put some blood into a monkey's peritoneal cavity and see what happens. It is extremely difficult for me to admit the possibility that endometriosis could result from metaplasia and develop the exact picture of normal endometrial epithelium and stroma, both in the peritoneum and the ovary.

I want to thank the discussants for their very intelligent and helpful suggestions, and in closing I would like to read one paragraph from the *Transactions* of this Society, Volume 51, page 102, 1926, at which the debate took place originally: "Dr. Sampson's theory would be greatly strengthened if he could demonstrate two things: First, the capacity of the degenerated epithelium given off at menstruation to grow in tissue culture; second, the capacity of such endometrium to grow on the peritoneum or ovary of the human being or perhaps even of one of the lower animals. Both of these proofs are lacking and because of the innate difficulties I am inclined to believe it will be difficult to prove either point experimentally." The author? Emil Novak of Baltimore.

(Papers by Drs. Lowenstein, Pick, and Philpott, Drs. Tysoe and Lowenstein, and Drs. Beacham and Beacham will appear in the December issue of the JOURNAL.)

Department of Case Reports New Instruments, Etc.

CONSIDERATION OF THE INFANT IN THE TREATMENT OF CERVICAL CARCINOMA IN PREGNANCY*

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(From the Department of Obstetrics and Gynecology, Kansas City General Hospital No. 2)

THIS 37-year-old Negro gravida v, para iii, whose last menstrual period was Sept. 1, 1948, and the estimated date of confinement June 8, 1949, was first seen in the outpatient clinic on Feb. 15, 1949. She gave a history of postcoital bleeding first noticed on Sept. 6, 1948. At this visit, the uterine fundus was 17.5 cm. above the symphysis and the fetal heartbeat was clearly heard. The general physical examination was not unusual except for the pelvic findings. The cervix showed a large, friable everting-type lesion that bled easily on contact and was about 4 cm. in diameter. The fornices did not seem to be narrowed. No palpable involvement of the anterior vaginal wall or rectovaginal septum was noted. Rectal examination revealed the right parametrium to be clear. There was questionable slight induration of the left parametrium. No palpable adenopathy was noted. Biopsy of the cervix revealed squamous-cell carcinoma, Grade 2. Clinically the lesion was considered to be a League of Nations Group II.

The patient was hospitalized on March 14, 1949, and on the following day a radium implantation was done, with the use of five 15-mg. capsules in sponge rubber with three capsules arranged about the periphery of the cervix and two capsules flat across the mid-portion. The total dosage was 3,600 mg. hr. Prior to the radium implantation, an external version was done, changing the fetus from left occipitoanterior to a transverse position, with the fetal head on the left. A tight binder was applied to hold the fetus in position. This was done to increase the distance between the infant and the radium sources and thereby to gain the advantage of the decrease in effective irradiation to the infant.

On March 23, 1949, the patient was again hospitalized because of a severe hemorrhage following a douche. She received four transfusions of 500 c.c. of whole blood during the week that she was hospitalized.

On April 21, 1949, she was readmitted to await delivery. Prior to operation, she had prophylactic penicillin. At 36 weeks' gestation, on May 10, 1949, a classical section, bilateral salpingo-oophorectomy, and supracervical hysterectomy were done with the delivery of a 4 pound, 14 ounce female infant. No palpable evidence of metastasis was present. The infant showed a halolike area of depilation on the right parietal region but otherwise seemed normal.

The patient was readmitted on July 4, 1949, for a radium implant because she had been very unfaithful in returning for deep x-ray therapy. On July 7, 1949, a radium implant was done using eight 3.3-mg. interstitial needles and a tandem of 30 mg. for 80 hours and a total dose of 4,512 mg. hr. The patient was not seen again until Dec. 27, 1949, at which time she returned to the Gynecologic Tumor Clinic. Examination at this time revealed the cervix to be practically obliterated at the apex of the vagina, with parametrial induration

*Presented at the joint meeting of the Chicago Gynecological, St. Louis Gynecological, and the Kansas City Obstetrical and Gynecological Societies, April 15, 1950.

about two-thirds of the way to the pelvic wall on both sides. Palpable involvement of bladder or rectum was not noted. The infant at this time exhibited a normal growth of hair and on physical examination was normal.

Calculations as to the effective amount of gamma irradiation to the infant in this case are based on the known distance between the radium sources and the fetal skull as measured on the x-ray films, and the temporary depilatory effect of that dosage on the infant. The average corrected distance of the sources of radium and the nearest surface of the fetal skull was 10 cm. The total amount of radium used was 75 mg. It was in place for 48 hours for a dosage of 3,600 mg. hr. The active length of each of the five 15-mg. capsules which were screened with 1 mm. of platinum was 1.8 cm. Calculated from this data, the maximum amount of irradiation delivered to the fetal skull would be about 300 gamma roentgens. This is in satisfactory agreement with the expected amount of irradiation needed to produce the temporary depilation that this infant had. It would be very interesting to check these results against the findings from a phantom setup with the same physical factors, since an appreciable degree of error may occur in the projection of such a curve as was necessary in these calculations.

Summary

The incidence of carcinoma of the cervix complicating pregnancy is such that the individual physician's experience in its management is very limited. The treatment of cases, in which the conservation of the infant is a consideration, presents many difficult and as yet unanswered problems. A considerable amount of data is available in the literature as to the radium dosage used in terms of milligram hours to the cervical lesion, but information concerning the effective dose at the level of the infant in terms of depth dosage, with a correlation with the effect on the infant of such amount of irradiation, has not been sufficiently explored and recorded.

1. Carcinoma of the cervix seen in the latter part of the middle trimester of pregnancy should be treated with radium therapy rather than deep x-ray therapy if conservation of the infant is desired.
2. In keeping with the inverse-square law, which is that the intensity varies inversely as the square of the distance from the source of irradiation, any procedure to increase the distance between the radium source and the infant is of definite value. The use of radiographs to determine this distance is of great importance.
3. In order to arrive at a definite conclusion as to the amount of gamma irradiation that can safely be administered without compromising the status of the infant, it will be necessary to have accurate long-term follow-up on the infants from cases in which all the physical factors of the irradiation treatment are known.
4. A case report is presented of a patient treated at 28 weeks' gestation in which the nearest surface of the infant was exposed to 300 gamma roentgens without any permanent untoward effect to date.
5. Accumulation and evaluation of data, as above presented, should provide valuable information as to the amount of gamma irradiation that can safely be employed for cases in which preservation of the infant is desired.

FEMALE GENITAL TUBERCULOSIS TREATED WITH STREPTOMYCIN

SAMUEL LUBIN, M.D., F.A.C.S., AND RICHARD WALTMAN, M.D., F.A.C.S.,
BROOKLYN, N. Y.

(From the Obstetrical and Gynecological Department, Cumberland Hospital)

TUBERCULOSIS of the female genitals involving the cervix and endometrium is a relatively uncommon condition and is usually secondary to a focus elsewhere in the body.

The treatment in the past has consisted of radical surgery, radiation therapy, and heliotherapy with sanatorium care. In the recent literature we have noted but three case reports^{1, 2, 3} utilizing streptomycin for this condition. Two cases involved the endometrium alone and the third the cervix alone. All three were apparently cured with this antibiotic. These cases were all apparently primary genital tuberculosis.

We are reporting a case of tuberculosis of the vault of the vagina, cervix, and endometrium treated with streptomycin continuously for a period of three months without an apparent cure. In this case the tuberculosis of the genitals was secondary to extrapulmonary tuberculosis.

G. D., a 24-year-old Negro woman, gravida 0, was admitted to the hospital complaining of vaginal bleeding of several days' duration, associated with night sweats and afternoon fever. The family history was essentially negative as both parents were living and well and showed no tuberculous contacts. The past history revealed an attack of pleurisy in 1944 and removal of a cervical lymph node in 1945.

From October, 1945, to December, 1946, the patient had been hospitalized at Sea View Hospital where the discharge diagnosis was extrapulmonary tuberculosis involving the lymph nodes of the neck, mesenteric lymph nodes, pelvic organs, urinary bladder, and peritoneum. Roentgen films of the chest were consistently negative for tuberculosis, and the sputum and gastric contents were repeatedly negative for tubercle bacilli. During the patient's stay in Sea View Hospital an exploratory laparotomy was performed.

In April of 1948 the patient complained of nocturia and dysuria and she was examined by the Urological Service at the Cumberland Hospital. Cystoscopic and radiographic examination of the genitourinary tract showed no evidence of tuberculosis. Guinea pig inoculation of the urine was also found negative for tubercle bacillus.

The present gynecological history disclosed that the menses had begun at 15 years of age, recurred regularly every 28 days, and lasted 3 to 4 days. The periods were perfectly regular until December, 1945. From that time to January, 1948, the patient was amenorrheic; at that time she had one regular menstrual period and none since.

The patient appeared at the Gynecological Clinic in July, 1948, complaining of vaginal bleeding. Examination at that time revealed a nulliparous marital introitus with no evidence of external infection. The uterus seemed normal in size and anterior in position, and the adnexa were not enlarged or tender. Speculum examination disclosed a fungating, granulating cauliflower-like protuberant mass which was excavated in the center and occupied the region of the cervix, with extension to the right fornix. The crater measured about 2.5 cm. in diameter. The region of the external os was studded with many papillary excrescences which bled easily. Biopsy of the cervix taken at this time revealed an epithelioid granuloma of the cervix, probably tuberculous in character. A Frei test was reported as negative.

On admission to the hospital on Aug. 16, 1948, the patient did not appear acutely ill, but rather underfed. General physical examination revealed no significant findings other than a scar on the left side of the neck and a lower midline abdominal scar from previous surgery.

Repeated biopsy of the cervix on Aug. 21, 1948, disclosed the following: tissue in the cervix showed polypoid hyperplasia of its lining. Beneath the lining there was an intense chronic inflammation with numerous epithelioid tubercles and occasional small abscesses with suggestive early caseous necrosis. The impression was granulomatous cervicitis, probably tuberculous (Fig. 1).

On Aug. 22, 1948, streptomycin therapy was instituted, consisting of 0.5 Gm. twice a day intramuscularly, and continued for three months. Pelvic examination at the inception of this therapy was essentially unchanged. A diagnostic dilatation and curettage were performed on Sept. 10, 1948, and a moderate amount of yellow, grayish, friable, mucuslike tissue was obtained. The pathological report showed areas of epithelial cells characteristic of epithelioid tubercles. There were multiple masses of necrotic tissue in areas, suggestive of caseation. The diagnosis was epithelioid granuloma with caseous necrosis, probably tuberculous (Fig. 2). A stain performed showed no tubercle bacilli.

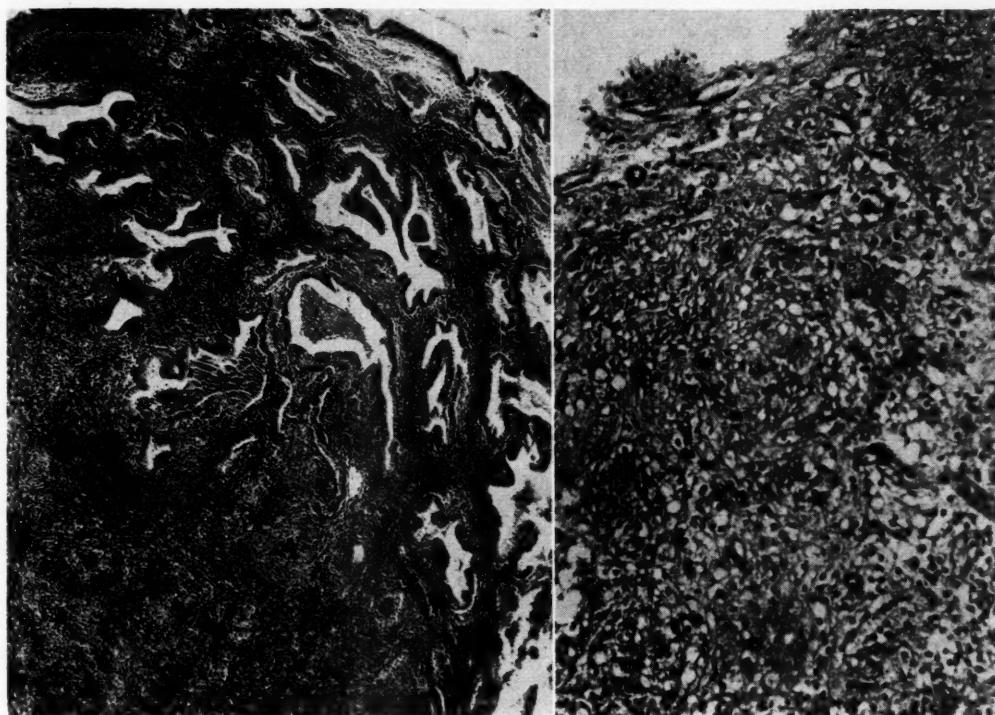


Fig. 1.

Fig. 2.

Fig. 1.—Section through cervix. Note the epithelioid tubercles, some with Langhans giant cells (arrow) in them, situated immediately beneath the mucosa (A) as well as in the wall of the cervix (B). ($\times 45$.)

Fig. 2.—Biopsy of endometrium. Note the epithelioid cells in the granulation tissue showing tendency to tubercle formation. ($\times 200$.)

Clinically, from the onset of streptomycin therapy, the patient's general condition seemed to improve. She gained 7 pounds in the first three weeks, her outlook was brighter, and she had no complaints except for a slight vaginal discharge. Speculum examination of the cervix on Sept. 21, 1948, after one month of therapy, revealed a remarkable change. The granulomatous cervix appeared smaller and the ulcerated area in the vaginal vault had diminished markedly in size, and its margin no longer appeared to be punched out. Streptomycin was continued and the patient was kept on a high-calorie and high-vitamin diet.

An endometrial biopsy was performed on Oct. 21, 1948, after two months of streptomycin therapy, and disclosed endometrial fragments enmeshed in large areas of coagulation necrosis with vague outlines of pre-existing structure discernible. At the periphery of these necrotic

areas there were small zones containing epithelioid cells. On Oct. 27, 1948, after ten weeks of streptomycin therapy, during the entire time of which the patient was afebrile and up and about, re-examination of the pelvis showed that the cervix was irregular in outline and high in the vaginal vault with a moderate amount of ulceration still present.

An exploratory laparotomy was performed two days later under spinal anesthesia, and healed peritoneal as well as mesenteric tuberculous glands were found. Because of the extensive dense adhesions between the intestines, the urinary bladder, and the pelvic organs, which were not visualized, it was deemed advisable not to attempt further surgery, and the abdomen was closed. The operative wound healed by primary intention and the streptomycin was supplemented with penicillin for the first week postoperatively. The postoperative course was uneventful and the patient was discharged to the clinic for follow-up after three months of streptomycin therapy, after receiving a total of 90 Gm.

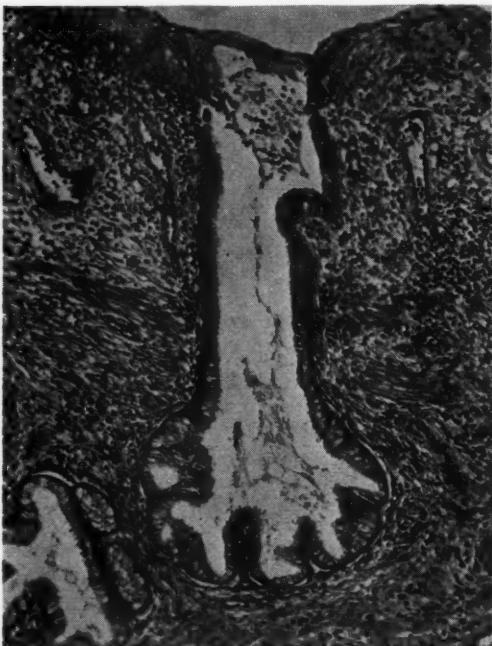


Fig. 3.



Fig. 4.

Fig. 3.—Cervix 13 months after initial streptomycin therapy. Note mild chronic inflammatory infiltrate immediately beneath mucosa. There is no evidence of tuberculous inflammation. ($\times 100$.)

Fig. 4.—Biopsy of endometrium 13 months after initial streptomycin therapy. Note tuberculous granulation tissue containing a giant-cell tubercle and caseation necrosis in the deeper layers of the section. ($\times 100$.)

Laboratory data showed a hemoglobin between 74 and 84 per cent with red blood cells varying from 3.3 million to 3.9 million. Repeated white blood cell counts varied between 7 and 8 thousand with a normal differential. The Kline test was negative. Acid-fast smears of the sputum were repeatedly negative and several roentgen-ray examinations of the chest revealed no evidence of pulmonary tuberculosis. The temperature was within the normal range throughout the entire hospital stay except for one week postoperatively, during which time it varied from 100° to 101.8° F. During the operation the patient was given a transfusion of 500 c.c. of whole blood.

The patient was seen in the clinic on numerous occasions since her discharge from the hospital on Nov. 22, 1948. The most recent cervical and endometrial biopsy, taken on Sept. 21, 1949 (Figs. 3 and 4), still showed evidence of tuberculosis, although the cervix appeared clinically healed.

Summary.—A case of endometrial and cervical tuberculosis, secondary to extrapulmonary tuberculosis, treated with streptomycin continuously for three months, is reported. While clinically the patient is improved and has no complaints, the microscopic evidence of the infectious process still persists in the cervix and endometrium.

References

1. Arkinson, A., and Dwight, R. W.: New England J. Med. 240: 294, 1949.
2. Michaelson, E. T., and Murray, P. M.: New York State J. Med. 49: 2433, 1949.
3. Schaupp, Karl L.: West. J. Surg. 57: 7243, 1949.

Correspondence

The Surgical Treatment of Carcinoma of the Cervix

To the Editor:

The renewed interest in the surgical treatment of carcinoma of the cervix must not be construed to indicate that, in the modern viewpoint, the surgical treatment is preferable to treatment by irradiation. This is certainly not the case. As emphasized repeatedly by those interested in the problem, the surgical treatment is being re-examined in certain institutions. It cannot be stated now that operation is the treatment of choice. Irradiation therapy remains as the treatment of choice for carcinoma of the cervix in general hands and this point cannot be overemphasized.

The strongest argument favoring irradiation therapy over surgery years ago was the high mortality incident to surgical operation in contrast to the low immediate mortality for irradiation. Now that the surgical mortality can be greatly reduced it is only natural that an interest in the surgical approach be revived. Carcinoma of the cervix can be cured by irradiation in a high incidence when the disease is sharply localized to the cervix. Irradiation therapy can afford effective palliation in advanced stages of the disease. Likewise, in view of the lowered surgical mortality that can now be achieved under favorable circumstances, the status of the surgical treatment cannot be regarded to have been finally settled on the basis of experiences two and three decades ago.

The simple total hysterectomy is wholly inadequate surgical therapy for carcinoma of the cervix. The so-called classical Wertheim operation does not represent the maximal surgical effort possible for attack upon cancer of the cervix.

Any attempt to cope with cancer of the cervix by these operations will lead to results that might well discredit a surgical attack upon the disease. The operation of radical panhysterectomy with pelvic node excision is a difficult procedure and should not be attempted by the occasional operator nor should it be attempted by those not well qualified in pelvic surgery and those not able by experience and training to cope with the surgical problems of the rectal colon and lower urinary tract.

As has been stated previously by others, the evaluation of a modern surgical approach to cancer of the cervix will require several years and must be confined to certain centers. If experience should prove that the surgical attack has certain advantages, there will then arise the problem of training gynecologic surgeons in the broad field of pelvic surgery (including surgery of the colon and genitourinary tract) and about this question much might be written.

Then, of course, there is the problem of the possible combined surgical and radiological treatment and just what combination will be most advantageous in which patients.

For the present it is timely, in the writer's opinion, to reiterate the principle that the standard treatment in general hands for cancer of the cervix is irradiation as this method is capable of curing favorable cases and should entail a minimum of immediate morbidity and mortality.

ALEXANDER BRUNSCHWIG, M.D.

MEMORIAL HOSPITAL, NEW YORK
AUGUST 1, 1950

The Urinary Bladder During Labor

To the Editor:

Some of the conclusions which Cohn and Weinberg reached as a result of their investigations, and published in the August, 1950, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, are open to question. Although their work was somewhat similar though less extensive than ours, their interpretation of the results was very different.

1. They recommend routine catheterization prior to instrumental delivery even though they noted that any pressure on fluid in the pelvic component of the bladder causes it to flow into the abdominal portion. Moreover, they agree that the abdominal portion is not the site of injury.

2. They state that bladder distention has no prophylactic value against injury to the lower urinary tract. Careful review of their paper fails to substantiate this conclusion. This is contrary to our impression, and our reasons will be listed later.

3. The cases of obstetric injury which they presented do not include a description of the status of the bladder at the time of delivery. They must, therefore, be relevant only to the bladder injury portion of their paper.

4. They found from cystographic studies taken during the first and second stages of labor that the bladder has both abdominal and pelvic components. This does not represent the complete picture of the bladder during labor. Its location during delivery, a matter of prime importance, was not included in this study.

We pointed out two important features which I should like to stress.¹ They are essential for understanding the physiology of the bladder during labor.

a. The location of the bladder depends wholly on the extent to which the pelvis is filled by the fetus. A cystogram taken with the head on the perineum, or with small parts completely filling the pelvis, either after the head has been delivered or with the breech on the pelvic floor, reveals no visible pelvic component. The urethra is longer and the bladder is almost entirely an abdominal organ. Therefore, since obstructive features are absent, catheterization is *not* essential.

b. There is a marked hypotonicity of the bladder during parturition. For this reason, pressure on any part causes fluid to pass to another. Moreover, when fluid is present within a hollow viscus, pressure on any portion is transmitted equally and undiminished (Pascal) to all other portions. Any pressure on the pelvic portion is thus transmitted to the abdominal! This must result in a diminution of direct traumatic effort.

In view of these facts, I should like to recommend to the authors additional cystographic studies, to correlate the bladder location with pelvic filling by fetal parts, and also cystometric studies during labor. With a knowledge of both, it would seem more prudent *not* to employ routine catheterization if the presenting part is near or on the pelvic floor.

HERMAN I. KANTOR, M.D.

DALLAS, TEXAS
SEPT. 8, 1950

Reference

1. Kantor, H. I., Miller, J. E., and Dunlap, J. C.: AM. J. OBST. & GYNEC. 58: 354, 1949.

Reply By Dr. Sidney Cohn

To the Editor:

Kantor has objected to our conclusions on essentially two counts. The first is based on his theory that the bladder becomes entirely an abdominal organ during labor, with lengthening of the urethra.¹ This is open to question. If it were true one would reasonably expect that forceps injuries to the urinary tract would be, in the main, urethral, rather than vesical, as they are. Our study² revealed a persistent pelvic portion of bladder dur-

ing the second stage of labor. Malpas and his associates,³ reviewing the classical frozen sections, demonstrated a persistent retropubic portion of bladder and no significant elongation of the urethra, with the single exception of a neglected impacted transverse presentation. They summarized their cystogram studies as follows, ". . . some part of the bladder usually remains behind the symphysis pubis throughout labour, and there is little if any elongation of the urethra." Besides the above evidence, a review of the paper of Kantor, Miller, and Dunlap, raises certain doubts. The "wholly abdominal" location of the bladder is demonstrated only at the very end of the second stage, when the pelvis is full. All parties agree that fluid is readily displaced from the pelvic portion of the bladder, when compressed, into the abdominal component. It is entirely reasonable, therefore, that cystograms taken with the pelvis full and the radiopaque fluid displaced from the pelvic portion of the bladder will reveal only the abdominal portion. It would be unwarranted to assume from such pictures that the pelvic component no longer existed. Apparently such an assumption was made, visualization of only the abdominal portion of the bladder being accepted as "bladder wholly abdominal." Some doubt as to this point was probably in the authors' minds as well, since they describe essentially the same location of bladder shadow in two separate illustrations as ". . . elevation of bladder fluid to abdominal portion" in the one case, and as ". . . bladder wholly abdominal" in the other.

The evidence would seem to indicate that some portion of the bladder remains in the pelvis and susceptible to injury during most forceps deliveries. Kantor and his associates agree that distention of the bladder will not alter the location of the pelvic portion.¹ Therefore, it is apparent that bladder distention can exert no prophylactic effect against forceps injury by removing the bladder from the zone of compression.

Kantor's second point concerns the so-called "cushioning effect" of fluid within the bladder. Since fluid is readily displaced from the compressed pelvic portion into the abdominal, and since the bladder is hypotonic, it is difficult to understand how the presence of urine within the bladder (short of extreme overdistention) can possibly prevent the anterior blade of a forceps from compressing or lacerating the bladder base against the pubis. Therefore, it would seem that no prophylactic effect against forceps injury of the bladder can be expected of a policy of noncatheterization. I agree with the statement that catheterization is usually not essential, since it is unlikely that a moderate accumulation of urine within the bladder during forceps delivery will produce any ill effect. However, on occasion, hyperdistention may be overlooked. Therefore, in general it would appear preferable to catheterize the parturient prior to forceps extraction.

SIDNEY COHN, M.D.

NEW YORK, N. Y.

SEPT. 28, 1950

References

1. Kantor, H. I., Miller, J. E., and Dunlap, J. C.: AM. J. OBST. & GYNEC. 58: 354, 1949.
2. Cohn, S., and Weinberg, A.: AM. J. OBST. & GYNEC. 60: 363, 1950.
3. Malpas, P., Jeffcoate, T. N. A., and Lister, U. M.: J. Obst. & Gynaec. Brit. Emp. 56: 949, 1949.

Dosage of Stilbestrol

To the Editor:

Dr. O. W. Smith in an article published in the November, 1948, issue of the JOURNAL gave her experiences with stilbestrol used for the prevention and treatment of some of the complications of pregnancy. She stated, "We have been concerned about the theoretical dangers of stilbestrol overdosage." In discussing the 10 cases of failure in the series of habitual abortions, she states that 9 were on too low a dosage, of whom 3 aborted and 13 were on "too high a dosage," 7 of whom aborted.

While the number of cases reported is substantial and while the writer has no dispute as to too low a dosage of stilbestrol being a cause of failure, he begs to differ from Smith in her viewpoint in regard to so-called unphysiologic dosage. It has been found that the larger the dose, the more certain the patient would carry the baby to term and deliver a normal child. What is the required dosage of stilbestrol? The writer has been interested in the correct reply to this question ever since he observed that stilbestrol is of value for threatened and habitual abortion and premature labor, somewhat over ten years ago. No definite dosage schedule is followed because the dosage varies with each individual, therefore no weekly increase is necessary. The amount required for the treatment of threatened abortion is that amount which stops cramps, low back pains, spotting, bleeding, and/or pain and keeps these symptoms from returning. Most patients require 25 to 50 mg. every morning.

Even though I have found no dosage schedule, the following is the amount that has been required in most cases to control the various types of threatened abortion. However we do not hesitate to give much larger doses if required to control the symptoms.

In threatened abortions, mild cases (patient with spotting, mild cramping, and low back pains for 4 to 12 hours): One hundred mg. of micronized stilbestrol are given every 15 minutes until symptoms are relieved and then 25 mg. three times daily for one week. Twenty-five mg. are given every morning until the eighth month. If pain, cramps, or bleeding recur, repeat above.

In moderately severe threatened abortion (cramps, low back pains, spotting and bleeding for 12 to 24 hours before treatment): Give 250 to 500 mg. of micronized stilbestrol in oil intramuscularly in the gluteal region, using a large spinal needle. Two hundred mg. of micronized stilbestrol are given orally every 15 minutes until all symptoms are controlled. 125 mg. tablet is given four times daily for two weeks, one tablet three times daily for 2 weeks, two daily in the morning for one week, and one daily thereafter until the eighth month. Every 3 to 7 days 250 to 500 mg. in oil intramuscularly are given for 2 to 4 times. Emergency dose of 50 to 200 mg. (two to eight 25 mg. tablets of micronized stilbestrol) is given immediately if symptoms or signs recur and treatment above is repeated. Find daily morning dose necessary to keep patient from aborting.

Severe type of threatened abortion (cramping, low back pains, bleeding, and pain 2 to 4 or more days before treatment): Give 250 to 1,000 mg. by mouth every 15 minutes until pain, cramps, and bleeding stop, followed by 250 to 500 mg. intramuscularly about every third day for 2 to 4 weeks, 100 mg. four times a day for two weeks, 25 mg. four times daily for 2 months, then one 25 mg. tablet daily until the eighth month.

In 64 consecutive private cases of threatened abortion of all types, 45, or 70 per cent, carried to term and delivered normal infants.

Habitual abortion: Twenty-five mg. of micronized stilbestrol are given upon rising and as soon as the patient has missed 3 to 7 days of menstruation and if her basal temperature indicates pregnancy. If the patient develops no signs or symptoms in 3½ months, ¼ of a 25 mg. tablet is given every morning. If the patient ever threatens to abort she is treated as a threatened abortion case as described above. Stilbestrol was given in this manner to 4 habitual abortion patients who had lost 24 babies (an average of 6 each). None aborted in this very small series.

Premature labor: It has been shown in our clinic that 200 mg. or more of micronized stilbestrol daily are required to keep the patient from losing her baby in a premature labor case. As soon as a premature labor starts, eight 25 mg. micronized stilbestrol tablets are given stat. and four every 15 minutes until all symptoms and signs disappear, plus 10 c.c. of stilbestrol in oil intramuscularly, which is repeated daily or every other day if signs or symptoms are not controlled. Then 300 to 400 mg. are given daily for one week and thereafter 200 mg. daily until the eighth month. If signs and symptoms of premature labor recur, the treatment is repeated. If history of premature labor is given, 25 mg. of micronized stilbestrol are given as soon as pregnancy is diagnosed and this dosage is continued until the eighth month. Emergency treatment is given if necessary.

In successfully treated sterility cases: All sterility patients who subsequently become pregnant are given 6.25 mg. of micronized stilbestrol as soon as pregnancy is diagnosed by basal body temperature, amenorrhea, frog test, or the Aschheim-Zondek test. If a patient ever threatens to abort she is treated for threatened abortion as previously described. It has been observed that before stilbestrol administration 27 out of every 100 such patients aborted but since stilbestrol is given 14 out of 100 abort.

Again I would like to emphasize that, in my opinion, no specific dosage schedule can be set up for stilbestrol in abortion cases, the dosage varies with each and every individual. Find the dose that holds the pregnancy and keep up this dose. No weekly or monthly increase has been necessary.

KARL JOHN KARNAKY, M.D.

329 MEDICAL ARTS BUILDING
HOUSTON, TEXAS
Oct. 7, 1950

Erratum

In the article, "Trichomonas Vaginalis Vaginitis: Treatment With a New Surface-Active Trichomonacide," by J. Mason Hundley, Jr., William K. Diehl, Herman Shelanski, and Robert L. Stone, in the October issue of the JOURNAL, the last sentence in the fourth paragraph on page 849 should read, "For clinic work, where it is so difficult to get patients to return for regular treatment, a therapeutic regime that proved 73 per cent successful in only one week's time is of particular significance."

Items

The Royal College of Obstetricians and Gynaecologists

At a recent convocation of the Royal College of Obstetricians and Gynaecologists, held in London, Honorary Fellowship was conferred upon Dr. George W. Kosmak, founder and editor of the JOURNAL.

American Board of Obstetrics and Gynecology

Notice to Candidates in or Entering Military Service

The present national emergency and remobilization justify certain broadening of the regulations for the benefit of candidates for certification by the American Board of Obstetrics and Gynecology, entering or in military service. Reference should be made to pages 8, 9, and 10 of the June, 1950, issue of this Board's Bulletin for comparison with present rulings cited below.

1. A man whose residency or preceptorship training in obstetrics-gynecology is interrupted by his entrance into military service may later request and receive six months' training credit for a hospital surgical assignment while serving with the Armed Forces. If his assignment is in obstetrics-gynecology under conditions acceptable to the Credentials Committee, he may request and be given more credit, subject to ruling of the Credentials Committee, toward his three (3) required years of formal specialty training.

2. A memorandum from the Office of The Secretary of Defense (7 August, 1950) states approved policy as follows:

a. During the current emergency all medical officers, except interns, assigned to Armed Forces medical facilities will be in a duty status.

b. All officers desiring specialty Board credit will be required to maintain a record of their professional work authenticated by an appropriate senior officer. The specialty Boards will be requested to grant credit for residency training for the work done in a specialty during this period.

This Board's regulations have anticipated the foregoing and remain the same as heretofore, namely,

"An applicant serving under military orders in an Army or a Navy hospital in an obstetrical-gynecological service under supervision will be given the same credit as if he were working under a preceptor, if these departments are supervised by Diplomates of this Board or recognized obstetricians-gynecologists. He may obtain full residency credit if such hospital is officially approved and listed for residency training in this specialty (and if the direction or supervision of its work is such that it can maintain its residency-type status and thus retain its formal approval). The Credentials Committee of the Board will review and give consideration to each individual case. Special request must be made for such credits."

Thus, Officers of the Regular services of the Armed Forces who had been working under a residency assignment, or Officers of the Reserve whose civilian residencies are interrupted, may offer an assignment to duty status in the specialty as described above, as substitute for their former residency appointments.

3. Periods of military service during the present emergency can be offered by candidates to apply full time toward the requirement of two (2) years of posttraining practice limited to the specialty.

4. Officers of the Armed Forces should inform the proper authorities of the extent of their specialty training in order to receive due professional qualifications credit and classification. In certain instances classification may have direct bearing on assignments.

Forms for Appraisal of Incomplete Training are available from this Board's Office, and may be used as evidence of present training status.

All candidates in military service should keep a careful, authenticated record of their professional work. Booklets for this purpose are being prepared for all specialties.

For Bulletin of Requirements, for forms, or other information apply to

PAUL TITUS, M.D., Secretary
American Board of Obstetrics and Gynecology
1015 Highland Building
Pittsburgh 6, Pa.

Notice to Hospitals Conducting Residencies in Obstetrics-Gynecology

On account of unsettled conditions associated with the Korean crisis and remobilization of the Armed Forces, the American Board of Obstetrics and Gynecology has voted to postpone indefinitely published plans for equal balancing of minimal residency training periods in obstetrics and in gynecology. Therefore, the paragraph in the current (1950) Bulletin of this Board, on page 7, reading "Effective January 1, 1954, training in each branch must balance to provide a minimum of eighteen (18) months each in obstetrics and in gynecology toward the required total of three (3) years" is deleted from present requirements.

The requirement of bilateral training in both obstetrics and gynecology is continued, but these need not be equally balanced as yet. A minimum of one year's training in the minor branch of a candidate's work thus continues to meet Board requirements.

Candidates are also notified that the present published requirement applying to age of case records (see page 16 of Bulletin) has been extended to allow reports of patients treated within five (5) years instead of four (4) years of the date of the candidate's application.

For further details, interested hospital administrators or candidates should refer to the Bulletin obtainable upon application at the Office of the Board:

1015 Highland Building
Pittsburgh 6, Pennsylvania

International Congress on Gynecology

The International Congress of the French Society of Gynecology is to be held in Paris, France, June 23 to 29, 1951, under the patronage of the President of the Republic. For further information address the General Secretary of the Congress, Prof. Claude Béclère, 23 Rue d'Artois, Paris 8^e, France.

German Gynecological Society

The next Congress of the German Gynecological Society will be held at Bad Pyrmont, Germany, April 4 to 7, 1951, under the presidency of Prof. H. Martius, Director of the University Clinic for Women, Göttingen, Germany.